METHYL BROMIDE

RISK CHARACTERIZATION DOCUMENT

Volume I

INHALATION EXPOSURE

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Environmental Monitoring and Pest Management Branches
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TABLE OF CONTENTS

FOREWORD

The Risk Characterization Document for Methyl Bromide is consists of three volumes. These volumes addresses the risk of human exposure to methyl bromide from inhalation (Volume I), oral (Volume II), or both routes (Volume III) of exposure. The introduction and toxicology in Volume I are applicable to Volumes II and III. These latter two volumes are currently being prepared. A document flow chart is provided on page vi. The risk from methyl bromide exposure is expressed as a margin of exposure which involves the consideration of both the toxicology and the human exposure levels under various scenarios. The calculated margins of exposures are used by the risk management to determine if mitigation measures are needed to modify the existing uses. For methyl bromide, the benchmark is a margin of exposure of 100; that is the human exposure should be 100-fold lower than the dose which did not cause any effect in experimental animals. Risk mitigation may be needed for any exposure with a MOE of less than 100. Reference concentrations are also provided in these documents and they are estimates of exposure levels to the human population that are likely to be without an appreciable risk. They are based on the toxicology and incorporated factors to account for uncertainty in the data. For methyl bromide, one such reference concentration is 210 ppb which has been used to develop the DPR permit conditions and regulations for acute inhalation exposure to methyl bromide.

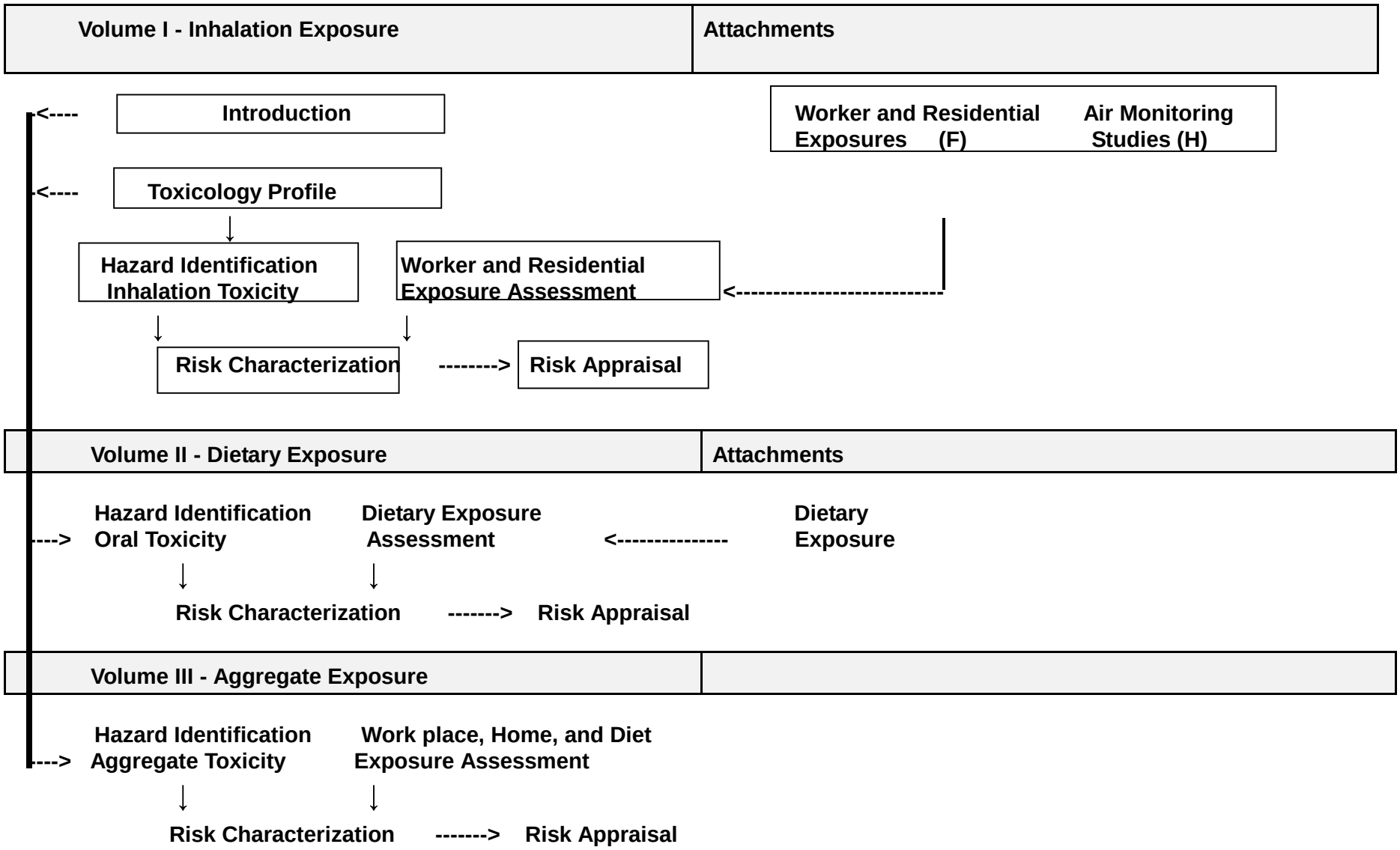
This Volume I on inhalation exposure supercedes previous documents on this subject. The DPR 1992 Preliminary Risk Assessment addressed only the acute and subchronic inhalation toxicity of methyl bromide (Attachment A). The toxicology data were limited in a document prepared for the Proposition 65 Developmental and Reproductive Toxicant Identification Committee (Attachment B). A 1998 preliminary draft of the Toxicology Profile and Hazard Identification sections was reviewed by the U.S. Environmental Protection Agency and Dr. Gerald Last, Professor at the University of California at Davis. A March 1999 draft was reviewed by the Office of Environmental Health Hazard Assessment (California Environmental Protection Agency) and the U.S. Environmental Protection Agency. Based on comments from these reviews, a draft of the risk characterization document for inhalation exposure was completed in October 1999 (DPR, 1999; refer to as “draft RCD/1999” in this Volume) and was made available to the public and was reviewed by the National Research Council Methyl Bromide Subcommittee in 1999-2000, under the mandate of Senate Bill 1320[1].

This document is a revision of the October 1999 draft and incorporated NRC comments as well as other needed changes to reflect current information. Overall, the major change was in the exposure assessment while there was no change in the critical endpoints or No-Observed-Effects Levels for risk characterization. A summary of the changes and the associated sections in the document is presented in the following table.

[1] SB1320 mandate for external peer review of the scientific portions of rules establishing a regulatory level, standard, or other requirement for the protection of public health and the environment.

Section	Revisions to the draft RCD/1999
FOREWORD	A new section was added to give background information and changes made since the draft RCD/1999 and a document organization chart.
I. TECHNICAL SUMMARY	Revised to reflect changes in the main text.
II. INTRODUCTION	**II.B.**- Updated regulatory information. **II.C.** and **II.D.**- Updated use information.
III. TOXICOLOGY	No change in the endpoints or NOELs.
IV. RISK CHARACTER-IZATION	**IV.A.1.**- No change in the critical endpoints or critical NOELs. **IV.A.2.d.** -Added discussion on the oncogenicity. **IV.B.** - The worker exposure estimates were revised to reflect only work conditions allowed under the current DPR permit conditions/regulations. In addition, an upper bound level or 210 ppb, rather than the highest measured value, was used for acute worker exposure. The residential exposure section was also revised to include ambient monitoring results and estimates of exposure based on modeling and distributional analysis of buffer zone air concentrations. **IV.C.**- Margins of exposures were recalculated based on revised exposure values.
V. RISK APPRAISAL	**V.A. and B.**-No change in these sections **V.C.**-Revised discussion on the uncertainties in the worker and residential exposure data. **V.D.2.** -Added discussion on polymorphism.
VI. CONCLUSIONS	Revised to reflect changes in the main text.

DOCUMENT ORGANIZATION



LIST OF TABLES

I. TECHNICAL SUMMARY

I.A. INTRODUCTION

In 1992, the Department of Pesticide Regulation (DPR) conducted a Preliminary Risk Assessment on methyl bromide to address acute inhalation exposures of residents reentering fumigated home. The risk assessment concluded that the reentry level of 5 ppm for residents posed a health hazard and an emergency regulation was promulgated to decrease the exposure. Subsequently, permit conditions were developed to reduce the acute exposure of workers and the residents living near fumigated fields and fumigation chambers. In 1999, a draft of the risk characterization for inhalation of methyl bromide was completed. This draft was reviewed by the National Research Council. This Volume I of the Risk Characterization Document is a revision of the 1999 draft.

I.A.1. Chemical Identification

Methyl bromide is a gaseous fumigant that kills insects, rodents, nematodes, weeds, and organisms that cause plant diseases. Since methyl bromide is released into the air during and after its use, there is a potential for exposure by the workers as well the general population living near the use sites. Methyl bromide is a restricted use pesticide for structural, soil, and commodity fumigations. In 2001, 54 products containing methyl bromide were registered in California. From 1996-1999, 11-16 million pounds were used each year in California.

The primary route of human exposure to methyl bromide is inhalation. Exposure may occur from accidental spills, drift, leakage, or residual levels of methyl bromide released after treatment. Signs and symptoms of inhalation exposure depend on the concentration and exposure duration. Early symptoms of acute exposure to lethal concentrations include: malaise, headache, visual disturbances, nausea, and vomiting. Later symptoms include delirium, convulsions, and respiratory failure or cardiovascular collapse leading to death. Nonlethal exposures result in neurological effects similar to the early symptoms for fatal exposure. These symptoms may persist after exposure, depending on the severity of the effects. Exposure of skin to methyl bromide results in vesication and swelling of the skin. The general population may also be exposed to methyl bromide-treated foods.

Since methyl bromide is acutely toxic, chloropicrin has been added to some methyl bromide formulations as a warning agent. However, there may not be a correlation between methyl bromide concentration in the air and the extent of the irritation induced by chloropicrin due to the differences in physical and chemical properties between these compounds. Also, chloropicrin itself is acutely toxic. With its increased use as a replacement for methyl bromide, there are increased concerns regarding the health effects from chloropicrin exposure.

I.A.2. Regulatory History

The Federal agencies have established regulatory levels for the uses of methyl bromide. For food uses, the U.S. Environmental Protection Agency (U.S. EPA) established tolerances based on inorganic bromide with the assumption that methyl bromide is completely degraded. The U.S. EPA oral chronic reference dose (RfD) is 0.0014 mg/kg/day. In the drinking water, the one-day, ten-day, and longer-term health advisories are 0.1 mg/L for children. The longer-term health advisory is 0.5 mg/L for an adult. The lifetime health advisory is 0.01 mg/L.

For methyl bromide in the air, the U.S. EPA inhalation reference concentration (RfC) is 5×10^{-3} mg/m^3. The Agency for Toxic Substances and Diseases Registry minimum risk levels (MRLs) are 50 ppb, 50 ppb, and 5 ppb for acute, intermediate, and chronic exposure scenarios, respectively. For occupational exposure, the federal Occupation Safety and Health Administration permissible exposure limit (PEL) is 20 ppm while California established a lower limit of 5 ppm and a ceiling of 20 ppm. The reentry level is 1 ppm for structural fumigation within the wall voids. Methyl bromide is a Class I ozone depleter and its use is regulated by the U.S. Clean Air Act and the United Nations Montreal Protocol.

In California, the use of methyl bromide is continually being evaluated as regulations/permit conditions are modified to limit exposures. Additional exposure data are being developed in 2001-2002 to determine seasonal (subchronic) exposures. The need for the permit conditions was initially based on the Preliminary Risk Assessment conducted in 1992 to address potential health hazard associated with acute exposures after structural fumigation (Attachment A). In 1993, methyl bromide, as a structural fumigant, was administratively listed as a developmental toxicant by the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency under Proposition 65 via the provision for listing due to the federal label warning requirement. However, the Proposition 65 Developmental and Reproductive Toxicity Identification Committee decided not to expand the listing to all uses of methyl bromide because results from laboratory animals did not “clearly” show that methyl bromide was a developmental toxicant.

I.A.3. Environmental Fate

Methyl bromide is degraded in the environment. The rate of hydrolysis was enhanced by elevated temperature, ultraviolet irradiation, aerobic conditions, and high organic matter in the soil. Once applied to the soil, methyl bromide volatilized into the air or adsorbed onto soil particles. Because of degradation, methyl bromide residues were not detected in the groundwater or commodities grown on fumigated soil. Residues were found in treated commodities after post-harvest fumigation.

I.B. TOXICOLOGY PROFILE

I.B.1. Pharmacokinetics

Pharmacokinetic studies showed that after inhalation, intraperitoneal, and oral administrations, methyl bromide was rapidly absorbed and radioactivity (^{14}C) was distributed to all tissues. With inhalation exposure, the percentages of the administered doses absorbed were similar in several species; they were 48% in the rat, 40% in the dog, and 52 to 55% in human. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure. With oral and intraperitoneal administration to rats, more than 90% of the dose was absorbed, with the highest radioactivity levels measured in the liver, kidneys, and testes. Methyl bromide was extensively biotransformed into unidentified products and carbon dioxide. In the rat, within 1 hour after inhalation exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. In humans, both methyl bromide and inorganic bromide were detected in the tissues 5 hours after a lethal dose exposure. The primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for oral exposure. Carbon

dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity in the exhaled air. After oral administration, biliary metabolites of methyl bromide were reabsorbed from the gut.

I.B.2. Acute Toxicity

Methyl bromide is a Toxicity Category I compound because of its acute inhalation toxicity. Severe irritation to eyes, skin, and mucous membranes occur after acute exposure; therefore, acute oral, ocular and dermal studies are not required for registration. Neurotoxicity has been observed in humans and laboratory animals after inhalation exposure to methyl bromide. The severity of the effects depended on the dose and duration of exposure. In humans exposed to high concentrations, neurological effects included ataxia, convulsion, and tremors. The nonlethal effects observed in laboratory animals included changes in brain catecholamines and tyrosine hydroxylase activity, tissue degeneration (nasal, brain, and adrenal glands), and neurotoxicity (ataxia and paralysis). Signs of oral toxicity in the dog included prostration, increased heart rates, lesions in multiple organs including the stomach and brain, hypoactivity, hypothermia, and death. Human dermal exposure resulted in skin lesions.

I.B.3. Subchronic Toxicity

Subchronic inhalation exposure of laboratory animals to methyl bromide resulted in altered brain catecholamine levels, decreased brain tyrosine hydroxylase activity, neurotoxicity, tissue degeneration (brain, nasal cavity, heart, testes, adrenal glands, thymus, spleen, and kidneys), and death. Based on overt signs of neurotoxicity, the dog, rabbit, and monkey were more sensitive to methyl bromide than other species (rat, mouse, and guinea pig). The primary finding after repeated oral exposure by gavage in the rat was hyperplasia of the forestomach. A decrease in body weight gain and food consumption was observed in rats given micro-encapsulated methyl bromide mixed in the feed.

I.B.4. Chronic Toxicity

The nasal cavity, brain, and heart were major target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage (hyperplasia, metaplasia, and necrosis) and myocardial degeneration were observed in rats and mice. Cerebellar and cerebral degenerations were detected in mice while reduced brain weight was observed in rats. When rats were exposed to methyl bromide in microcapsules mixed in the feed, the primary effect was body weight reduction. Possible treatment-related lesions were found in the spleen, liver, pancreas, and lungs. In male dogs given methyl bromide-fumigated feed, decreased hematocrit and hemoglobin levels were observed.

I.B.5. Genotoxicity

Methyl bromide was genotoxic in several *in vitro* and *in vivo* assays. It was a base-pair substitution mutagen in the *Salmonella* assays. It was a direct-acting mutagen since a liver S-9 fraction was not required for mutagenicity. It caused micronuclei formation in female mice and an increased frequency of sister chromatid exchanges in CHO cells and in mouse bone marrow cells *in vivo*. It did not induce unscheduled DNA synthesis in rat hepatocytes or cause sperm abnormalities in mice. DNA alkylation was detected in both rats and mice after *in vivo*

exposure by oral, intraperitoneal, or inhalation routes while DNA damage was found in the germ cells of rats after inhalation exposure. There was some evidence of genotoxicity in workers exposed to methyl bromide. Elevated levels of sister chromatid exchanges in lymphocytes and S-methylcysteine adducts in the blood were measured in soil fumigators. An increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in the lymphocytes and an increased incidence of micronuclei in oropharyngeal cells were observed in structural fumigators.

I.B.6. Reproductive Toxicity

In a 2-generation reproductive toxicity study in rats by inhalation, methyl bromide reduced the fertility rate of the F_1 parents during the second mating trial. While the body weights of the treated pups at birth showed varied responses, their body weights were significantly lowered during lactation. Brain weight and cerebral cortex width were reduced in the F_1 parents.

I.B.7. Developmental Toxicity

Methyl bromide caused developmental effects in both rats and rabbits after inhalation exposure. The findings in the fetuses included delayed skull ossification in rats and fused sternebrae, gall bladder agenesis, and other effects in rabbits. Methyl bromide did not cause any significant developmental effects in rats and rabbits after oral exposure.

I.C. RISK ASSESSMENT FOR INHALATION EXPOSURE

I.C.1. Hazard Identification for Inhalation Exposure

The evaluation of risks from exposure to methyl bromide followed the four steps of risk assessment: hazard identification, dose-response assessment, exposure evaluation, and risk characterization. In the hazard identification and dose-response assessment, a comprehensive review of the toxicology database from studies submitted by the registrant and published articles was conducted. From this review, the toxicity and the estimates of how much methyl bromide that could potentially cause an adverse effect as well as no-effect levels are identified for each study. Since human case reports did not provide sufficient details to derive the critical no-observed-effect levels (NOELs), results from experimental animal studies were used assuming that the effects observed in the animals would also be observed in humans. The NOELs were expressed as human equivalents (adult or child) to correct for the difference in respiration rates between humans and experimental animals. The studies with most relevant findings for risk assessment were then selected and the associated NOELs were expressed as critical NOELs to be used in the calculation of the margin of exposure (MOE) in the risk characterization step of the process. For methyl bromide, critical NOELs were determined for acute (one-time exposure), short-term (1-2 weeks), subchronic (7-13 weeks, seasonal), and chronic (a year or more) exposures. The National Research Council scientists (NRC) in their review of the draft RCD/1999 agreed with DPR selection of critical endpoints and NOELs for risk characterization.

For acute exposure, neurotoxicity is the primary effect of concern and has been observed in both experimental animals and humans. The clinical signs observed include: decreased activity, ataxia, paralysis, convulsion, and tremors. Of the laboratory animals studied, there was a species sensitivity to the neurotoxicity of methyl bromide after short-term exposure. Based on

the comparisons of the lowest-observed-effect level (LOEL) for neurotoxicity, the dog and rabbit showed greater sensitivity than the guinea pig, mouse and rat. For example, dogs exposed to 156 ppm (human equivalent level of 68 ppm) showed severe neurological effects in 2 to 7 days of exposure while rats exposed to the same concentration in terms of human equivalent level (65 ppm; 70 ppm actual air concentration) for the same exposure duration did not show any neurotoxicity. In pregnant animals, the rabbit was more sensitive to methyl bromide than the rat. For pregnant rabbits, severe neurotoxicity was observed at the LOEL of 70 ppm (Sikov *et al.*, 1981; Breslin *et al.*, 1990) while no neurotoxicity was reported in the pregnant rats at the same level (Sikov *et al.*, 1981).

The selection of results from the most sensitive species, in this case the dog, is consistent with the U.S. EPA Neurotoxicity Risk Assessment guidelines (U.S. EPA, 1998a). The critical NOEL was 103 ppm from short-term inhalation studies in the dog (Newton, 1994a and b). At this dose of 103 ppm, no effects were observed until the 8th day of exposure. Although the dog inhalation toxicity studies were not designed to be a neurotoxicity study as defined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guideline, they were conducted under Good Laboratory Practices and DPR considered the results valid for hazard identification. These same data were used by the Methyl Bromide Industry Panel (MBIP) to support their position that a chronic inhalation toxicity study in the dog should not be required (CMA, 1994).

The selection of the 103 ppm dose as the acute NOEL considered three major factors: subjectiveness of the observations, severity of the neurotoxicity at higher concentrations, and possibility of delayed neurotoxicity. The finding of no effect at 103 ppm in the dogs was based on gross observations. Neurotoxicity may have been present but not detected unless more refined methods such as the Functional Observation Battery were used. Therefore it is possible that the actual NOEL may be lower than 103 ppm. Furthermore, severe neurotoxicity was observed at higher doses (1.5 times the NOEL) with a few additional days of exposure. At 156 ppm, one of two dogs showed lacrimation (tearing) on the first day. This finding by itself may arguably be considered less significant with respect to adversity. However, there were only two dogs in this group. With 2-3 days of additional exposure, there was significant toxicity as both dogs showed difficulty breathing and decreased activity. In another study, all dogs (8 in the group) exposed to 158 ppm showed decreased activity before the end of the second exposure day. With 5 additional days of exposure, all showed severe neurotoxicity and brain lesions. The selection of 103 ppm as the acute NOEL also addresses, indirectly, the possibility of delayed neurotoxicity which has been reported in humans after accidental poisonings. Since no effects were observed in the dogs at 103 ppm for 7 days of continuous exposure, it is unlikely that there would be delayed neurotoxicity within one week after a single exposure to the same level. The human equivalent NOEL (25 ppm) from the dog study was two-fold or less than those for the acute effects observed in the rats and guinea pigs.

Another endpoint DPR considered for acute exposure risk assessment is the developmental toxicity observed in experimental animals after methyl bromide exposure. In a developmental toxicity study, the pregnant animals were exposed continuously to methyl bromide during a specified period of gestation (when organ formation occurs). Any adverse effect observed in the fetus is considered an acute effect under the current assumption that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. Environmental Protection Agency Guidelines for Developmental Toxicity Risk Assessment. Since this endpoint is the result of exposure during pregnancy, it is

only used for the assessment of exposure by women of childbearing age in the work force and the general population.

The critical NOEL for developmental toxicity was 40 ppm from a study with rabbits (Breslin *et al.*, 1990). The result from this study was the basis for the emergency regulation and permit conditions currently used in California. U.S. EPA also considered these endpoints of concern and has used the same study in a Section 18 evaluation on the use of methyl bromide on imported fruits at ports of entry. In this rabbit developmental toxicity study, fetuses exposed to 80 ppm *in utero* showed gall bladder agenesis (no gall bladders), fused sternebrae (early fusion of the sternebrae), and lowered body weights. The missing gallbladder finding was seen in Part I of the experiment, which by itself is a complete study and fulfilled FIFRA guidelines for an acceptable study. The investigator was concerned with the finding as it was rarely observed in the negative-control litters in the conducting laboratory as well as in other laboratories using the same rabbit strain. When the experiment (Part II) was repeated three months later, missing gall bladders were again observed in fetuses exposed to methyl bromide *in utero*. The fused sternebrae found in Part I was not confirmed since a skeletal examination was not performed in Part II.

The developmental toxicity effects observed in fetuses should not be discounted because of maternal toxicity (body weight changes and neurotoxicity) reported at the same dose level. Consideration must be given to when the effects were observed. First, the decrease in the body weight gain of the 80 ppm group does was not a consistent finding. Statistically significant decreases were reported for gestation days 13-16 in Part I and gestation days 7-20 and 10-13 periods in Part II. The reduced weight gain in the does of Part II occurred concomitantly with a reduction in the mean fetal body weight. Second, there was no significant difference in the strictly maternal parameter calculated as the terminal body weight minus gravid uterine weight. Third, body weight changes in pregnant rabbits are known to be more variable than in rodents. As a result, body weight changes often do not carry as much support as an indicator for maternal toxicity as for rodents as discussed in the U.S. EPA Developmental Toxicity Risk Assessment guidelines. Fourth, maternal neurotoxicity was characterized by clinical signs, including: lethargy, head tilt, slight ataxia and slight lateral recumbency. These signs were observed in only 3 of 43 does (7%) dosed at 80 ppm, and they did not appear until gestation days 19-20 (the last days of the 13-day exposure period). Based on the description and comparison with observations reported in other studies, DPR does not consider these signs as indicators of excessive toxicity.

Furthermore, the failure of gall bladders to form in some fetuses was independent of maternal neurotoxicity. In Part I, 6 of the fetuses with missing gallbladders were from 3 does without neurotoxicity while the remaining 7 affected fetuses were from 2 does with neurotoxicity. In Part II, none of the does showed neurotoxicity while 4 fetuses (from 4 does) had missing gallbladders. In addition, the development of the gall bladder in rabbits can be considered an acute event since it takes place in one to two days after its onset on gestation day 11.5 (Hoar and Monie, 1981). The maternal neurotoxicity reported on gestation days 19-20 would have occurred too late to have been a factor in the agenesis of the gall bladder.

Similar findings have not been reported in the rat developmental toxicity studies. While it is worth noting that rats do not have gall bladders, the absence of these findings in another species should not negate their significance as indicators of the potential for methyl bromide to

cause developmental toxicity in humans. Species specificity in developmental effects has been demonstrated for some chemicals. Developmental toxicity testing under FIFRA guidelines requires two species to be tested, a rodent and a non-rodent species, typically the rabbit, for identifying species susceptibility. The need to test non-rodent species arose from the findings of thalidomide where it was demonstrated that this human teratogen did not exhibit significant teratological effects in rats but caused at least some significant effects in rabbits (Schardein, 1985). As stated in the U.S. EPA Developmental Toxicity Risk Assessment guidelines, developmental effects may not be evident in more than one species. The findings from the most sensitive species are appropriate to use to estimate human risk.

The significance of the developmental toxicity findings was discussed in a 1994 Proposition 65 meeting to determine whether methyl bromide should be listed for all uses. The emergency regulation in 1992 resulted in methyl bromide being listed as a chemical known to the State of California to be a reproductive toxicant. The Developmental and Reproductive Toxicity Identification (DART) Committee was presented with results from animal developmental toxicity (absence of gall bladders and fused sternebrae) and reproductive toxicity (decreased pup body weight) studies. After much discussion, the Committee voted not to expand the listing of methyl bromide from structural fumigation to all uses because there was not enough evidence to support the “clearly shown” criteria as mandated by the Proposition. However, the members expressed several concerns: the need for more experimental studies to clarify the findings, potential for exposure to methyl bromide via the milk during lactation, and the lack of information on human exposure especially during pregnancy.

After this meeting, DPR received additional data to support the consideration of reproductive or developmental toxicity as a pertinent endpoint for risk assessment and regulatory actions. First, supplemental data on the rat reproductive toxicity study showed that methyl bromide caused a reduction in the width of a certain part of the brain (cerebral cortex) in the F_1 adults exposed to methyl bromide *in utero* (American Biogenics Corp., 1986). Second, a study received by DPR in 1998 showed that methyl bromide caused a breakage of DNA in the testicular cells isolated from rats after inhalation exposure (Bentley, 1994). It is not known whether the effect was due to methyl bromide or a metabolite.

DPR also considered studies which showed that methyl bromide caused biochemical changes in the brain which may be associated with neurotoxicity. In the rat, acute exposure to methyl bromide has been shown to alter catecholamine (chemicals involved in the transmission of brain signals) levels and tyrosine hydroxylase (an enzyme involved catecholamine formation) activity in the brain. However, an extensive review of the published articles on this subject by DPR showed inconsistencies in the findings; thus, they were considered not appropriate for use in the determination of regulatory levels. The results of one of these study were used by the Agency for Toxic Substances and Diseases Registry of the Public Health Service to derive a minimum risk level as a screening tool for regulatory agencies to determine the need for regulation. As such, the study review did not critically analyze the results. This minimum risk level has not been adopted as an action level by any regulatory agency.

Therefore, two acute NOELs were selected to address the different human sub-populations. The NOEL of 40 ppm for developmental toxicity in the rabbit was most appropriate for workers and residents since women of child bearing age are in both groups. For children, the NOEL was 103 ppm for neurotoxicity in the dog. When these NOELs are converted to

human equivalent NOELs taking into consideration of duration of exposure and the differences in the respiration rates between species, and between adults and children, the human equivalents were 21 ppm and 25 ppm, respectively, for developmental toxicity and neurotoxicity. The use of the lower human equivalent NOEL of 21 ppm compared to 25 ppm to address occupational and residential exposures would protect children from the effects of methyl bromide.

For short-term and subchronic exposures, neurotoxicity was also selected as the endpoint for the determination of the critical NOELs and was based on the same considerations as discussed for acute exposure. For short-term (1week) exposure, a NOEL was established to address the potential exposure of residents returning to fumigated homes, living near fumigated fields, and workers. The critical NOEL was 20 ppm based on neurotoxicity (convulsion, paresis) in the rabbit after exposure to 70 ppm for 1 week (Sikov *et al.*, 1981). Three of 26 does died after 9 to 10 days of exposure.

For subchronic exposures of longer duration (90 days, seasonal), the critical NOEL was an estimated NOEL (ENEL) of 0.5 ppm based on a lowest-observed-adverse-effect level (LOAEL) of 5 ppm for decreased responsiveness in two of eight dogs during a neurological examination after 6 weeks of exposure (30 exposure days) and a default factor of 10 for the calculation of a NOEL from a LOAEL (Newton, 1994b). While the duration is shorter than the 13-week generally considered for subchronic exposure, it was chosen because of the endpoint (neurotoxicity) and species sensitivity (the dog is a more sensitive species than the rat to methyl bromide) considerations. It is possible that the NOEL may be lower if the dogs were exposed to methyl bromide for 13 weeks.

This ENEL was lower than the NOEL (3 ppm) for lowered body weights of rat pups from dams exposed to methyl bromide before mating and during part of the pregnancy in the reproductive toxicity study (American Biogenics Corp., 1986). Another study also showed a NOEL (estimated) of 3 ppm based on a dose-related decrease in brain weight at 30 ppm and higher concentrations in the female rats (Norris *et al.*, 1993 a and b). The brain weight was also significantly decreased in the 140 ppm male rats. This effect on the brain weight was considered biologically significant since the brain is a target organ of methyl bromide. The absence of neurotoxicity by Functional Observational Battery testing at the same dose (30 ppm) does not diminish the importance of the brain weight finding since the causes of the two effects are not necessarily related.

For chronic inhalation exposure, all chronic studies conducted with rodents (rats and mice), reproductive toxicity study, and subchronic dog inhalation toxicity study were considered in the determination of the chronic critical NOEL. After chronic inhalation exposure, tissue damage was noted in the nasal cavity, brain, and heart of rodents. The critical NOEL was an ENEL of 0.3 ppm based on a LOAEL of 3 ppm for the induction of an increase in the number of cells (hyperplasia) and change in cell type and function (degeneration) in the nasal cavity of rats after 24-29 months of exposure and a default factor of 10 for the calculation of a NOEL from a LOAEL (Reuzel *et al.*, 1987 and 1991). While the exposure duration was considered a life-time for the rodents, the actual duration in the standard chronic toxicity studies is two years. Since humans may be exposed to methyl bromide on a yearly basis, not just one or two years in the lifetime, the NOEL from the chronic toxicity study after two years of exposure was, therefore, appropriate for use. This NOEL may underestimate the risk of repeated yearly exposure as

there is evidence of cumulative toxicity, in particular, neurotoxicity. The LOEL (3 ppm) from this 29-month study for nasal olfactory epithelial damage (Reuzel *et al.*, 1987 and 1991) is further supported by the LOEL of 4 ppm from a 24-month study for lesions at the same site (Gotoh *et al.*, 1994). The U.S. EPA also used the same LOAEL from this study in the determination of the chronic reference dose (RfC).

The significance of the finding in the nasal cavity is that it showed methyl bromide not only injured the cells but also changed the normal function of the cells in the nasal cavity. Such damage may result in the loss of the animal's sense of smell. Tissue damage in other organs occurred at higher concentrations. With acute exposure to 200 ppm, the damage to the rat olfactory epithelium included epithelial disruption, fragmentation, and exfoliation (Hurtt *et al.*, 1988). Repair of the epithelium included replacement by a squamous epithelium, loss of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). In other short-term studies, the damage to the nasal epithelium was described as necrosis and degeneration (Eustis *et al.*, 1988) and dysplasia (NTP, 1992; Eustis, 1992). In the chronic inhalation toxicity study, nasal olfactory epithelial hyperplasia and degeneration were observed in the rat (Reuzel *et al.*, 1987 and 1991).

While the effect on the nasal cavity may generally be considered a finding confined to the rat due to anatomical considerations, it is not the case with methyl bromide. Dogs exposed to 156 ppm methyl bromide for only 6 days showed moderate to moderately severe olfactory degeneration (Newton, 1994b). In addition, the rodent studies are the only available studies to evaluate the chronic toxicity. The requirement for a non-rodent (dog) study was waived by DPR based on the evaluation of short-term studies in the dog which showed that a chronic study would have to be conducted at relatively low dose levels. For comparison, the ENEL of 0.3 ppm for nasal cavity effects when expressed as human equivalent level (0.1 ppm) was the same as the human equivalent level for neurotoxicity after subchronic exposure (ENEL of 0.5 ppm). This implied that the actual NOEL for chronic exposure if based on neurotoxicity could be lower than that based on the effects in the nasal cavity. However, it is not possible to extrapolate such a NOEL at this time because the subchronic NOEL was already an estimated NOEL based on a LOEL which was reduced by a 10-fold uncertainty factor.

The oncogenicity of methyl bromide can not be evaluated at this time because experimental studies showed neither dose-related increased incidence of tumors after treatment nor sufficient data to determine the incidences. There is evidence that methyl bromide causes damage to the genetic material in experimental animals and humans, which is generally considered to play a significant role in the process of tumor formation.

A summary of the critical NOELs for inhalation exposure risk characterization is presented below:

Scenarios	Experimental NOEL	Human Equivalent NOEL[a]		Reference Concentration[d]	Effects in Animal Studies	Ref[e]
		Adult[b]	Child[c]			
Acute	40 ppm	21 ppm	na	210 ppb	Developmental toxicity (pregnant rabbit)	1*
	103 ppm[f]	45 ppm	25 ppm		Neurotoxicity (dog)	2
Subchronic 1 week	20 ppm	12 ppm	7 ppm	120 ppb(adult) 70 ppb (child)	Neurotoxicity (pregnant rabbit)	3
6 weeks	0.5 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Neurotoxicity (dog)	2
Chronic	0.3 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Nasal epithelial hyperplasia(rat)	4*

a/ Experimental NOELs were converted to human equivalents using equations in Attachment G. na= child equivalent NOEL were not calculated because the effects were observed in pregnant animals. ENEL=estimated NOEL and is 1/10 of the LOEL in the study.

b/ The adult equivalent NOELs are appropriate to address worker exposures. They are also used for residential exposures when child equivalent NOELs were not calculated.

c/ The child equivalent NOELs are appropriate to address resident exposures (see footnote b).

d/ The reference concentration was the ratio of the human equivalent NOEL and a default uncertainty factor of 100 since the NOEL was derived from experimental animal studies.

e/ * indicates study was acceptable to DPR according to FIFRA guidelines. References: 1. Breslin *et al.*, 1990b; 2. Newton, 1994b; 3. Sikov *et al.*, 1981; 4. Reuzel *et al.*, 1987 and 1991.

f/ The NOEL and human equivalents are presented in this Table for comparison purposes only. They are not used for risk characterization.

I.C.2. Exposure Assessment for Workers and Residents

Human exposure assessment was conducted for occupational and residential inhalation exposures to methyl bromide. Compared to the draft RCD/1999, this exposure assessment was revised to incorporate NRC recommendations and changes after re-evaluation of the database, methodology, and DPR regulations.

Occupational Exposure

The inhalation exposures of applicators in structural fumigation were not determined because they are required to wear self-contained breathing apparatus. No data were available for other workers such as tarp removers.

For field fumigation, monitoring studies were conducted primarily to determine the effectiveness of modifications to existing application procedures and aeration of treated fields. With shallow-shank and tarp fumigation, workers involved in the application with no modifications had higher exposures than those in other methods. The acute exposures of applicator, copilot, and shovel-man ranged from 188 ppb to 245 ppb. The best method involved both swept-back shank and closing shoes where the applicators, copilots, and shovel-men exposures were 1 ppb to 58 ppb. The driver (7 ppb) and copilot (62 ppb) of the tractor in the placement of tarp had lower acute exposures than those involved in the application. For tarp cutting and removal, one study showed acute exposures of 202 ppb and 215 ppb while another study showed workers with higher acute exposures (22 to 1058 ppb). With deep-shank injection, the applicators with only overhead fan had the highest acute exposure at 281 ppb. Lower acute exposures were measured for applicators in tractors with modifications such as overhead fan and scrapers and rollers (104 ppb), enclosed cab (161 ppb and 171 ppb), and enclosed cab with scrapers (13 ppb). When a second tractor with a disc or cultipacker was involved, the drivers had relatively lower exposure (13-181 ppb) than those for applicators, except for the disc driver (934 ppb). For both short-term and subchronic exposures in shallow-shank and deep-shank methods, the exposure patterns were similar to those for acute exposures which were the basis for the calculations. Chronic exposure was not expected for any of the work scenarios. For workers at adjacent fields, there were no data and their exposures were assumed to be at 210 ppb.

For workers with potting soil in greenhouses, the maximum acute exposure was 210 ppb. Their actual exposures were relatively low because tarp venters are required to wear self-containing breathing apparatus, and tarp removal occurs after 48 hours of venting. The short term exposures, based on measured values, were 0.001 ppb and 0.14 ppb for these two group of workers. No subchronic or chronic exposures were determined for this activity. No data were available for other workers, e.g., applicators, associated with this use.

For commodity fumigation workers, the acute exposure was 210 ppb and the exposures for other durations based on the average of measured values. For workers involved in the fumigation of grain products, the range of short-term exposures was 0.02 ppb to 11 ppb. The forklift drivers of sea containers/trailers had higher subchronic and chronic exposures (8 ppb) than those (3 ppb) for non-certifying fumigation chambers. For workers involved in the fumigation of raisins, the range of short-term exposures was 3 ppb to 180 ppb. For workers in a walnut processing plant, workers in clearing plant (178 ppb) and vacuum chamber (180 ppb) had

the highest short-term exposure compared to other areas. The lowest average short-term level (25 ppb) was measured in the special cracking area. For both raisin and walnut workers, the short-term and subchronic exposure levels were similar. Chronic exposure was considered for raisin processing workers but was not expected for most walnut processing workers.

For workers in a brewery, exposures were estimated for applicators and aerators at various locations. The acute exposure was assumed to be at 210 ppb. The short-term exposure level ranges were 7-49 ppb for aerators and 8-12 ppb for applicators. No seasonal or chronic exposures were expected.

For workers in the facilities but whose tasks were not directly related to commodity fumigation, data were available only for raisin and walnut fumigations. The exposure levels were either based on the acute level of 210 ppb or measured by ambient and area sampling. The range of short-term exposures ranged from 7 ppb to 180 ppb. The subchronic and chronic exposures (except for walnut processing) were comparable to those for short-term levels because of the frequency of exposure.

Residential Exposures

The exposures of residents returning to homes after fumigation and aeration were not estimated due to lack of data on current practices. DPR regulations limit the maximum acute exposure at 210 ppb.

Residential exposures to field fumigation were determined using monitoring data and computer modeling of the data. Maximum methyl bromide air concentration was related to the size of the field and emission rate (depending on the method of application). At the 95th percentile, the exposure ranges for each field sizes were: 161-174 ppb (1 acre), 163-215 ppb (10 acre), 201-225 ppb (20 acres), 213-230 ppb (30 acres), and 221-236 ppb (40 acres).

The acute exposure for residents living near commodity fumigation facilities was limited to 210 ppb. The exposures for the longer-term durations were 90-180 ppb (short-term), 70-175 ppb (subchronic), and 86-106 ppb (chronic).

For residents living in methyl bromide use areas which may include field, commodity, and structural fumigations, ambient air monitoring at the 95th percentile daily exposure levels ranged from 0.239 ppb (Mettler Fire Station) to 30.2 ppb (Pajaro Middle School in Watsonville). Levels at these two sites also provided the ranges for weekly (0.163 to 17.1 ppb), and 7-8 week (0.084 to 7.68 ppb) exposure durations. Additional monitoring has been conducted by the Air Resources Board and the registrant to characterize the exposures.

I.C.3. Risk Characterization for Inhalation Exposure

The NOEL at which adverse effects did not occur was used to assess the non-cancer hazard for potential human exposures to methyl bromide. The margin of exposure (MOE) was compared with a conventional benchmark level of 100. The MOEs varied from <1 to greater than 1000 for occupational and residential exposures.

Occupational Exposure

Margins of exposures were not calculated for workers involved in structural fumigation. The acute MOE for the applicators was assumed to be greater than 100 since these workers are required to be in a self-contained breathing apparatus.

With shallow-shank/tarp/broadcast fumigation, the acute MOEs were 112 (applicator), 86 (copilot), and 110 (shovel-man) for workers Noble plow and overhead fan. The MOEs were higher for the workers in shallow-shank/tarp/bed fumigation and various equipment modifications. The MOEs for these applicators were 144 to 5250 for swept-back shank and closing device. For copilots, the MOEs varied depending on the modification. The MOE was 69 when a conventional shank was used, even though scrapes/closing shoes were added. The MOEs were 111 when the copilot was in a raised platform and 362 when swept-back shank and closing device were used in the application. The MOEs for the driver and copilot in the second tractor for tarping were 3000 and 339, respectively. The MOEs for workers in tarp cutting and removal varied depending on the study even though similar procedures were used. In one study, the MOEs were 104 and 98; in the second study, the range of MOEs was 20 to 955. With deep-shank injection, the applicators with only overhead fan had the lowest MOE of 75. The range of MOEs were: 130 to 1614. The MOEs for driver in the second tractor with a cultipacker were also higher when scrapers were used after application. The MOE increased from 116 (no modifications) to 164-1615 (use of scrapers and/or rollers). The MOE was only 22 for the disc driver. For both shallow-shank and deep-shank methods, the MOEs for almost all short-term exposures were 100 while subchronic exposures were less than 100. Chronic exposure was not expected for any of the work scenarios. For workers at adjacent fields, the acute MOE could be assumed to be 100 with the exposure not to exceed 210 ppb.

The acute MOEs for all workers in commodity fumigation facilities were 100 because their upper exposure limit was 210 ppb. For tarp ventors and removers of potting soil fumigation in greenhouses, the MOEs for short-term exposures were greater than 80,000 because of their relatively low actual exposures . No data were available for other workers. In the fumigation of grain products, MOEs for these workers were greater than 100 for the aerators for all exposure periods. For forklift drivers, the short-term MOEs were > 1000 but the subchronic and chronic MOEs were less than 100 (MOEs of 25 and 67). For workers involved in the fumigation of raisins, the range of MOEs for short-term exposures was 67 to 4000. The MOE of 67 was based on the use of 210 ppb as the daily exposure value. The MOEs for subchronic and chronic exposures were less than 100, except for the forklift drivers with a MOE of 100. For workers in a walnut processing plant, the MOE was 67 for workers with the highest exposures (in clearing plant or vacuum chamber). This MOE was based on measured values (cleaning plant) and the 210 ppb limit (vacuum chamber). The highest MOE was 480 for workers at the special cracking area. The MOEs for subchronic and chronic exposures were less than 10. For workers in a brewery, the MOEs for applicators and aerators were ranged from 245 to 1714.

For workers in fumigation facilities, not directly related to fumigation, the short-term exposure MOEs were generally greater than 100 (MOE of 121 to 1714) for raisin facilities. The short-term MOE for walnut processing was 500 based on area sampling but was 67 based on 210 ppb as the daily exposure level in sorting and packaging areas. However, the subchronic and chronic exposure MOEs for both raisins and walnut processing facilities were less than 100 based on either measured values or 210 ppb.

Residential Exposure

For residents living in treated home after aeration, the acute MOEs were assumed to be at least 100 since regulations were based on the 210 ppb for acute exposure.

For residents living next to the buffer zone of field fumigation, the MOEs were 98 to 131 for the 95th percentile of methyl bromide air concentration determined for 1 and 10 acres field sizes and all emission rates. For 20 and 30 acres, the MOEs were around 100 (96 to 104) with the exception of 91 and 93 for 80 lbs emission rate. For 40 acres, the MOEs were 89 to 95 for all emission rates. At the 90th percentile air concentration, all MOEs were at or greater than 100.

The acute MOE for residents living near commodity fumigation facilities was 100 because the exposure was assumed to be 210 ppb. However, the MOEs were 39-78, 1, and 1, respectively, for short-term, subchronic, and chronic exposures based on 210 ppb as the average daily exposure levels.

For residents living around methyl bromide uses, ambient air monitoring of 12 sites showed MOEs ranged from 695 to >80,000 for acute exposure, and from 409 to > 40,000 for short-term exposures. For 7-8 weeks of exposure, the MOEs for 7 of the sites were greater than 100 (range form 126 to 1190). The MOEs for the remaining sites ranged from 13 (Pajaro Middle School) to 78 (Salinas Ambient Monitoring Station).

I.D. RISK APPRAISAL FOR INHALATION EXPOSURE

Certain limitations and uncertainties were incorporated into the hazard identification, exposure assessment, and risk characterization of methyl bromide.

I.D.1. Hazard Identification

For acute inhalation exposure to methyl bromide, the critical NOEL was based on developmental effects observed in rabbits with the assumption that methyl bromide will also cause developmental toxicity in humans. There are no data to support or refute this assumption. The reference concentration (210 ppb) for this NOEL was only 1.5-fold lower than that for neurotoxicity in humans (350 ppb). The endpoints for the critical short-term and subchronic exposures were based on neurotoxicity in the pregnant rabbit and dogs, respectively. There were uncertainties associated with the use of hyperplasia/degeneration to the nasal cavity of rats as the endpoint to evaluate chronic inhalation toxicity. One uncertainty was the interspecies variability in the nasal cavity between rodents and humans. Additional information on the pharmacokinetics of methyl bromide in the nasal cavity epithelium of animals and humans would permit additional consideration of this endpoint.

In this RCD, both the subchronic and chronic NOELs were estimated from the LOEL, the lowest dose tested. The estimated subchronic NOEL was 0.5 ppm based on neurotoxicity observed in two of eight dogs exposed to 5 ppm for 34 exposures. Due to limitation in the database, a default factor of 10 was used for the extrapolation. For chronic exposures, the estimated NOEL was 0.3 ppm based on a LOEL of 3 ppm for nasal epithelial hyperplasia and degeneration in the rat and an uncertainty factor of 10. The mildness of the lesion at the LOEL suggested that an UF of less than 10 might be sufficient to estimate the NOEL from the LOEL.

I.D.2. Inhalation Exposure Assessment

The major limitation in the worker (all uses) and residential (commodity fumigation) exposure assessment was that data were not available for many scenarios as some acute exposures were assumed to be or limited to 210 ppb. The use of 210 ppb exposures might be over- or underestimation of actual acute exposures. Of the available data, there were many deficiencies in the overall database and they included: small sample size, incomplete report, and short monitoring period. Potential areas of underestimation were the assumptions of single work task per day and no overtime worked. One area of overestimation was the use of 50% recovery value to adjust all data.

For residential exposure to field fumigation, there were also uncertainties in the determination of the maximum methyl bromide air concentration distribution along the buffer zone perimeter of fumigated fields. These uncertainties included: the precision and accuracy of the sampling and analytical methods, influence of environmental factors on air concentrations, application variability, use of default weather conditions, and use of default assumptions in estimating air concentrations associated with overlapping applications. Actual exposure may be underestimated or overestimated because of these uncertainties.

I.D.3. Risk Characterization

For risk characterization, the uncertainties included the use of uncertainty factors to address extrapolation of no-effects from experimental animals to humans (interspecies), and accounting for intraspecies variations. The sensitivity of humans and laboratory animals to methyl bromide toxicity was difficult to compare because of inadequate exposure information in human case reports. The current DPR default factor of 10-fold was used to address interspecies extrapolation. For intraspecies variation in the response to methyl bromide, the default uncertainty factor of 10 was also used because human illness/poisoning reports did not provide sufficient information to derive another factor. Studies on genetic polymorphism of glutathione-S-transferase (GST) in humans provided some evidence for variations in human response to methyl bromide. However, there were insufficient data to conclude that GSTT polymorphism leads to increased susceptibility to methyl bromide toxicity and to determine whether or not the variation is sufficiently addressed by the 10-fold default intra-individual uncertainty factor.

I.D.4. Issues related to the Food Quality Protection Act

There may be a potential for increased sensitivity of infants and children to the neurotoxicity of methyl bromide based on consideration of the maturity of the central nervous system. Given that methyl bromide is a potent neurotoxicant and there are no data on developmental toxicity, an additional uncertainty factor was suggested to address the potential increased sensitivity for infants and children. However, the NRC in the review of the draft RCD/1999 did not recommend such a factor mainly because the DPR selected NOELs for risk characterization that were considered adequately protective for these groups.

As for other Food Quality Protection Act issues, there could be a potential for aggregate exposure from occupation or residential exposures and dietary exposures. This aspect is being

addressed in a separate document. There is a potential for cumulative toxicity between methyl bromide and other alkylation agents. However, appropriate approaches are not available at this time. Based on available studies, methyl bromide has not been shown to cause endocrine disruption effects.

I.E. CONCLUSIONS FOR INHALATION EXPOSURE

The human health risk from potential inhalation exposure to methyl bromide was evaluated in this Volume I of Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: developmental toxicity for acute exposure, neurotoxicity for short-term and subchronic exposures, and tissue damage to the nasal cavity for chronic exposures. For acute and chronic exposure endpoints, neurotoxicity was also considered in the determination of the critical NOELs. The risks, expressed as the margins of exposure, were calculated for workers and residents involved or living in the vicinity of structural, field and commodity fumigations. Generally, a MOE of at least 100, which takes into account the possibility of 10-fold variations in susceptibility within the human population as well as between laboratory animals and humans, is considered adequate to protect humans from the effects of concern. Exposure scenarios with MOEs of less than 100 should be considered in the risk management process.

With structural fumigation, the acute MOEs for workers and residents were assumed to be at least 100 based on restrictions in the DPR regulations. However, data are needed to estimate actual exposures for acute and short-term exposures for workers and residents.

For field fumigation, the acute MOEs for workers were at or greater than 100 because of the most effective equipment modifications and work hour restrictions were placed in DPR regulations. However, there were work tasks with acute and short-term MOEs of less than 100 which are not specifically excluded in the regulations. They were: disc driver (acute MOE of 22, deep shank injection), and tractor drivers and basket-men in tarp removal (acute MOE of 20-21, tarp shallow with Noble plow shanks). For subchronic exposure, most of the worker tasks had MOEs of less than 100; many were less than 10 and included applicators, copilots, disc drivers, and tarp removers. The MOE for workers at adjacent fields was assumed to be 100 since they work outside of the buffer zone. Actual data are needed to verify this assumption as analyses for the effectiveness of buffer zones showed MOEs of less than 100 for some applications (in particular large fields and certain emission rates). For residents living at the buffer zone perimeter of fumigated fields, the acute MOEs were generally around 100 for the 95th percentile exposure except for a MOE of 91 for 30 acres and 80 lbs emission rate, and MOEs of 89-95 for 40 acres and all emission rates. The acute MOEs were generally greater than 100 at the 90% percentile exposure. No assessment was conducted for repeated exposures.

For commodity fumigation, the acute MOEs for workers involved in fumigation were at 100 because DPR regulation set work hour restrictions to limit the maximum exposure at 210 ppb. The actual MOEs were likely higher as the upper limit may not be reached in some scenarios. The short-term MOEs were greater than 100 for all work tasks based on actual measurements; the only exception was a MOE of 67 for the task of cleaning plant. The MOE was also 67 when the daily exposure was set at 210 ppb for raisin (clear chamber) and walnut (vacuum chamber) workers. The subchronic and chronic MOEs were generally less than 100

based on measured values and exposures amortized from 210 ppb.

For workers doing other tasks in commodity fumigation facilities, the acute MOEs and many of the short-term MOEs were at or greater than 100. The only exception was the short-term MOE of 67 for workers at the sorting or packaging areas and their exposures were based on 210 ppb as daily exposure. The subchronic and chronic MOEs for all workers were at or less than 67. Additional data are needed to characterize the exposures of these workers at the facilities. For residents living near fumigation facilities, the MOEs for all durations were based on 210 ppb used for acute exposure, and not actual measurements. The MOEs were between 1 and 78 for short-term, subchronic and chronic exposures.

The ambient air monitoring of three counties in California showed acute and short-term MOEs greater than 400. However, the 7-8 week MOEs were less than 100 (MOEs of 13 to 78) in some locations. Additional monitoring are being conducted to better characterize these exposures.

This risk assessment concluded that human inhalation exposure to methyl bromide resulted in margins of exposure of greater than 100 in some scenarios but less than 100 in other scenarios. The significance of these MOEs need to be viewed in the context of the limitations and uncertainties discussed. Many scenarios were based on exposure data with few samples or assumed exposure levels (i.e. 210 ppb for acute exposure). There were also scenarios which were not addressed in this document. Additional exposure data are needed to better characterize the exposure. In addition, the overall risk from methyl bromide exposure should consider the risks from other exposure routes. The risk characterization of dietary exposure and aggregate exposure is in Volumes II and III, respectively.

II. INTRODUCTION

A human health risk assessment for inhalation exposure to methyl bromide has been conducted because of adverse effects identified in chronic toxicity, oncogenicity, reproductive toxicity, developmental toxicity, genotoxicity, and neurotoxicity studies conducted with laboratory animals. The toxicity of methyl bromide in humans from occupational and accidental exposures also has been documented. Methyl bromide is regulated under the California Air Contaminant Act (AB 1807), The Food Safety Act (AB 2161), The Birth Defect Prevention Act of 1984 (SB 950), and Proposition 65. While the review of toxicology studies included all routes of exposure, the potential risk from dietary exposure to methyl bromide residues in the fumigated foods is addressed in a separate document.

II.A. CHEMICAL IDENTIFICATION

Methyl bromide has been used commercially since the 1890s (review by Alexeeff and Kilgore, 1983; WHO, 1995). Early uses were as an anesthetic agent, methylating agent, refrigerant, fire extinguishing agent, and fumigant. Currently, methyl bromide is used as a multipurpose fumigant for pest control in structures (warehouses, ships, freight cars, and homes) and in post-harvest treatment of commodities (Farm Chemicals Handbook, 1998). It is also used in the preplant treatment of soil in fields and greenhouses to control nematodes, insects, weeds, bacteria, and fungi. Methyl bromide is the primary fumigant for quarantine use on commodities exported to other countries (Attachment C).

The primary effect of methyl bromide after inhalation exposure is neurotoxicity which has been observed in both humans and laboratory animals (detailed discussion of the studies is in **III. TOXICOLOGICAL PROFILE**, and Attachment D). The signs and symptoms are dependent on concentration and exposure duration (von Oettingen, 1946; Rathus and Landy, 1961; Greenberg, 1971; Grant, 1974; Anger *et al.*, 1986; Gehring *et al.*, 1991; Uncini *et al.*,1990; De Haro *et al.*, 1997).

With dermal exposure, vesication and swelling of the skin and increased plasma bromide levels were observed in workers exposed to high concentration of methyl bromide (Butler *et al.*, 1945; Jordi, 1953; Zwaveling, *et al.*, 1987; Hezemans-Boer *et al.*, 1988).

II.A.1. Mechanism of Action

The exact mechanism for the toxicity of methyl bromide via the inhalation route is not known. Methyl bromide is an alkylating agent and has been shown to bind irreversibly to sulfhydryl groups *in vitro* (Lewis, 1948; Price, 1985). Gehring *et al.* (1991) suggested that the depletion of glutathione (GSH) observed in the study by Alexeeff and Kilgore (1985) was a result of methyl bromide-GSH conjugate formation. However, conjugated metabolites of methyl bromide have not been reported. The depletion of GSH may also be due to the inhibition of glutathione reductase activity (Jaskot *et al.*, 1988; Davenport *et al.*, 1992).

The effect of methyl bromide on brain GSH and GSH transferase has been proposed as the mechanism of neurotoxicity (Davenport *et al.*, 1992). Methyl bromide-induced locomotor effects (tremors, ataxia, and limb paralysis) may be a result of changes in brain GSH

metabolism (Orlowski and Karkowsky, 1976). In a case study of two workers, methyl bromide conjugation with GSH by GSH transferase was hypothesized to account for the severity of neurotoxicity observed (Garnier *et al.*, 1996). Other investigators suggested that methyl bromide-induced neurotoxicity was due to the decrease of catecholamine (norepinephrine and dopamine) levels and the inhibition of tyrosine hydroxylase activity in the brain (Honma *et al.*, 1982, 1987, and 1991). The decrease in catecholamine levels may cause reductions in presynaptic neuronal activity, feeding, and body temperature. This effect would be consistent with the decreased locomotor activity and weight loss observed in rats. In addition, an increase in the sensitivity of dopamine receptors after methyl bromide exposure has been suggested as the mechanism for the neurotoxicity symptoms (hallucination, insomnia, and delusions) (Honma *et al.*, 1994). Other indications of neurotoxicity observed in the rats were conditioned taste aversion (Miyagawa, 1982) and increased thiopental-induced sleep time (Honma *et al.*, 1985).

The toxicity observed in human and animal studies with low concentrations of methyl bromide is likely due to methyl bromide *per se* and not bromide. First, methyl bromide is more toxic than bromide. The rat oral LD_{50} (3,500 mg/kg) for sodium bromide is more than 15-fold higher than that (214 mg/kg) for methyl bromide (Smith and Hambourger, 1935; Danse *et al.*, 1984). For acute exposure, the lowest level of bromide in the blood that caused toxicity is 125 mg bromide/100 ml (Gosselin *et al.*, 1976). A no-effect level of 4 mg/kg based on electroencephalograph changes and increased thyroid activity in human volunteers and an average daily intake (ADI) of 1 mg/kg of sodium bromide has been proposed for humans (van Gelderen *et al.*, 1993). For chronic exposure to bromide, central nervous system effects (drowsiness, bizarre behavior, and hallucinations) were observed in a 60-year-old woman who ingested a bromide elixir daily for 7 years. The serum bromide level was 44.6 mEq/L (or 215 mg/100 ml based on 1 mEq=48 mg) (Blumberg and Neli, 1967).

Second, bromide level in the plasma, serum or urine is not an indicator of the severity of methyl bromide intoxication. The diet and past medicinal use of bromides contribute to the endogenous level of bromide (Harvey, 1985). Human studies and accidental poisoning cases showed that the bromide levels of affected individuals did not correlate with the symptoms (Drawneek *et al.*, 1964; Marraccini *et al.*, 1983; Squier *et al.*, 1992; Kishi *et al.*, 1991; Tanaka *et al.,* 1991). Hemodialysis did not alleviate the neurotoxic effects of methyl bromide in a worker accidentally exposed to methyl bromide while cleaning a rice silo (Moosa *et al.*, 1994). Hustinx *et al.* (1993) suggested that the severity of clinical signs is correlated more with previous exposures than serum bromide levels (more details about this study are in **III.H. NEUROTOXICITY**).

II.A.2. Chloropicrin

Chloropicrin, a lacrimator and a fumigant, is added to the formulations as a warning agent because methyl bromide is acutely toxic and is odorless. However, the efficacy of chloropicrin, which ranged from 0.25% to 67% depending on the formulation, has been questioned (WHO, 1995). Methyl bromide concentration may be 100-fold higher than that of chloropicrin because of the difference in vapor pressures and densities of these two compounds (Van Assche, 1971). The vapor pressure and density for methyl bromide are 1380 mm Hg and 3.78, respectively, and those for chloropicrin are 18.3 mm Hg and 5.68, respectively. At 1.3 ppm chloropicrin, which causes irritation, the calculated methyl bromide level was 115 ppm. The air

levels of these two compounds were measured simultaneously in a monitoring study conducted by the California Air Resources Board (Seiber *et al.*, 1987). After field fumigation with methyl bromide (194 lbs/acre) and chloropicrin (95 lbs/acre), the maximum methyl bromide and chloropicrin levels were: 1133 ppt for methyl bromide and 681 ppt for chloropicrin in the ambient air, and 900 ppb for methyl bromide and 23.8 ppb for chloropicrin 20 yards from the field.

The use of chloropicrin in California has increased from 2.1 million to 2.8 million pounds from 1993 to 1998 (DPR, 1993-1998). In 2000, a total of 3.9 million pounds were used (DPR, 2000a). Because of the increased use, in particularly as a replacement for methyl bromide, there is concern about the potential health effects from exposure. The risk characterization of chloropicrin is being prepared as a separate document and a summary of use and toxicity information is provided in Attachment E.

II.B. REGULATORY HISTORY

The insecticidal activity of methyl bromide was first reported in 1932 (Le Goupil, 1932). Methyl bromide is a restricted use pesticide in the United States. Retail sale and uses are limited to certified applicators or persons under their direct supervision, and only for those uses covered by the applicator's certification.

II.B.1. Ozone Depletion

Methyl bromide is an ozone depleter with a calculated ozone depletion potential (ODP) of 0.7 (Watson *et al.*, 1992). In the 1994 Science Assessment of Ozone Depletion document, a panel of atmospheric scientists concluded that methyl bromide continued to be a significant ozone depleter with an ODP of at least 0.3 (NOAA/NASA/UNEP/WMO, 1995). The worldwide sources of methyl bromide include: anthropogenic (human made) agriculture (20-60 kilotons/year), biomass burning (forest fires, grass fires) (10-50 kilotons/year), leaded gasoline burning (0.5-22 kilotons/year), and oceans (60-160 kilotons/year). There is evidence that methyl bromide produced by open oceans is reabsorbed. Therefore, methyl bromide from agriculture use is a significant source for human exposure. The amounts (as % applied) of methyl bromide used which eventually reach the atmosphere have been estimated to be: 50-95% for soil, 80-95% for post-harvest commodity, and 90% for structural uses (U.S. EPA, 1997a).

The concern of methyl bromide and other chemicals with ozone depleting potential (ODP > 0.2) is currently being addressed by the U.S. Clean Air Act and the United Nations Environment Programme Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol). Under the U.S. Clean Air Act, the U.S. Environmental Protection Agency (U.S. EPA) was required in 1994 to freeze the U.S. production and importation of methyl bromide at the 1991 level (U.S. EPA, 1993). A complete ban was scheduled for the year of 2001. However, the 1998 U.S. Congress passed legislation to extend the use until 2005. Recently, U.S. EPA determined that pesticide applicators using methyl bromide would not be required to use impermeable tarps to reduce air emissions from field fumigation because not enough was known about how the use of the tarps would affect crop production (U.S. EPA, 1998b). U.S. EPA recently published final rule on the exemptions for quarantine and preshipment uses of methyl bromide (U.S. EPA, 2001). These uses are permitted under the Montreal Protocol and exemptions are required by amendments to the Clean Air Act.

At the international level, the Parties (more than 125 nations) to the Montreal Protocol added methyl bromide to the list of depleters and agreed on deadlines for a freeze on the production and importation of methyl bromide (U.S. EPA, 1993). In 1997, Parties to the Montreal Protocol agreed to an extension of the use. The current deadlines for the 100% use reduction are 2005 and 2015 for developed and developing countries, respectively (UNEP, 1997). There are ongoing efforts to develop alternative approaches (GAO, 1996; USDA, 1993; CDFA, 1995; Braun and Supkoff, 1994).

II.B.2. Federal Regulations

The U.S. EPA established tolerances in commodities based on bromide level because of the assumption that methyl bromide is degraded completely to bromide (Federal Register, 1991a). However, residue studies have shown that fumigated commodities contain detectable levels (in ppm range) of methyl bromide especially immediately after fumigation. In 1986, the Methyl Bromide Industry Panel (MBIP) petitioned the U.S. EPA for tolerances for methyl bromide *per se* (U.S. EPA, 1986a). The proposed levels ranged from 0.1 ppm for certain vegetables to 5.0 ppm for green cocoa beans.

The U.S. EPA has established an oral chronic reference dose (RfD) and inhalation reference concentration (RfC) for methyl bromide (U.S. EPA, 1992a). The RfD is 0.0014 mg/kg/day based on the no-observed-effect level (NOEL) of 1.4 mg/kg/day for forestomach epithelial hyperplasia in a rat oral subchronic study (Danse *et al.,* 1984) and an uncertainty factor of 1000. The inhalation RfC is 5×10^{-3} mg/m^3 (1.3 ppb) based on the LOAEL of 3 ppm for nasal olfactory epithelial hyperplasia from a rat chronic inhalation study (Reuzel *et al.*, 1987 and 1991) and an uncertainty factor of 100. For methyl bromide in the drinking water, the one-day, ten-day, and longer-term health advisory for a child is 0.1 mg/L assuming 1 L/day water consumption for a 10-kg child (U.S. EPA, 1992a). The longer-term health advisory for an adult is 0.5 mg/L assuming 2 L/day water consumption for a 70-kg adult. The lifetime health advisory is 0.01 mg/L assuming 20% of exposure by drinking water. Methyl bromide is classified as a "Group D" carcinogen (not classifiable as to human carcinogenicity) by U.S. EPA due to inadequate human and animal data (U.S. EPA, 1992a).

The Agency for Toxic Substances and Disease Registry (ATSDR) has established minimal risk levels (MRLs) for methyl bromide which may be of concern at hazardous waste sites and releases (ATSDR, 1992 and 1996). The acute MRL is 0.05 ppm based on an acute NOEL of 16 ppm for decreases of brain tyrosine hydroxylase activity in the rat after 8 hours of exposure to 31 ppm (Honma *et al.*, 1987 and 1991) and adjusted for daily exposure and a 100-fold uncertainty factor for interspecies and intraspecies extrapolation (16 ppm x 8/24 x 1/100). The intermediate inhalation MRL is 0.05 ppm (5 ppm x 1/100) based on a NOEL of 5 ppm for a decrease in monoamines in the rat after 3 weeks of continuous daily exposure to 10 ppm (Honma *et al.*, 1982). The chronic MRL is 0.005 ppm (2.3 ppm x 1/10 x 8/24 x 5/7 x 1/10) based on increased prevalence of muscle aching and fatigue, increased sensitivity threshold, and lowered recall ability in an epidemiological study of workers with an average exposure of 2.3 ppm for 8 hours per day and 5 days per week (Anger *et al.*, 1986) and an uncertainty factor of 100 for extrapolation of LOEL to NOEL and intraspecies variation. Respiration rate differences between animals and humans are not accounted for in these MRLs. The intermediate oral MRL is 0.003 mg/kg/day based on gastrointestinal effects.

The National Institute for Occupational Safety and Health has determined an Immediately Dangerous to Life and Health Concentration (IDLH) for immediate evacuation of workers exposed to methyl bromide (NIOSH, 1997). The IDLH of 250 ppm was supposedly based on an acute inhalation toxicity data in humans (Clarke *et al.*, 1945). However, the air concentration was not measured in the cited human report. The federal Occupation Safety and Health Administration permissible exposure level (PEL) is 20 ppm (CFR, 1989). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value of 1 ppm (ACGIH, 1998).

II.B.3. California Regulations

In California, the use of methyl bromide is regulated by permit conditions and regulations promulgated by DPR[2].

Structural Fumigation

For occupational exposure to methyl bromide, the current California permissible exposure limit (PEL) for methyl bromide is 5 ppm or 20 mg/m^3 and a ceiling limit of 20 ppm (California Code of Regulations, 1998). A reentry level of 5 ppm following fumigation of homes was established under the Label Improvement Program for Fumigants (U.S. EPA, 1986b). All persons are required to wear a self-contained breathing apparatus (SCBA) or combination air-supplied/SCBA respirators at concentrations higher than 5 ppm. In 1992, an evaluation of the monitoring data and toxicology studies showed that the 5 ppm reentry level in fumigated homes did not provide a sufficient safety margin for human exposure (DPR, 1992; Attachment A Preliminary Risk Assessment). The DPR promulgated emergency regulations to require a longer aeration period and lowered the reentry level to 1 ppm in the wall voids, and pest control operators had to hand out a Fact Sheet explaining the potential human hazards of methyl bromide fumigation. The Fact Sheet was prepared by the DPR in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), California Department of Health Services, and U.S. EPA. A similar warning for developmental effects was subsequently required by U.S. EPA on methyl bromide product labels used for structural fumigation (U.S. EPA, 1992b).

On January 1, 1993, methyl bromide was administratively listed by OEHHA as a developmental toxicant under Proposition 65 via the provision for listing due to the federal label warning requirement. On December 21, 1993, OEHHA modified the listing from "methyl bromide" to "methyl bromide as a structural fumigant" because the Fact Sheet and label changes were limited to the use of methyl bromide as a structural fumigant. The Proposition 65 Developmental and Reproductive Toxicity Identification (DART) Committee of the OEHHA Science Advisory Board decided methyl bromide should not be listed for all uses since the evidence was considered equivocal[3] and did not support the “clearly shown” criteria as mandated by the Proposition (OEHHA, 1994) (additional discussion under **IV. RISK ASSESSMENT A.1.a. Developmental Toxicity**).

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[2] DPR web site: http://www.cdpr.ca.gov/docs/dprdocs/methbrom/mb_main.htm

[3] The National Toxicology Program defines equivocal as “marginal evidence which may be chemical related.”

In 2000, DPR adopted new regulations for structural fumigations (DPR, 2000b). The regulations set a minimum buffer zone of five feet (with longer buffer zones for larger applications), required tarpaulins of specific standards, and set specific safety standards for aeration of fumigated structures and tarp removal.

Field and Commodity Fumigation

Methyl bromide when used in agricultural production is classified as a restricted material. Possession and use of restricted materials are allowed only under a permit from the county agricultural commissioner. Before issuing a permit, the county agricultural commissioner must evaluate the application to determine whether it will cause environmental harm. Depending on the results of this review, the commissioner may deny the permit or impose permit conditions including the use of specified mitigation measures. In evaluating permit applications, commissioners must consider and, where appropriate, use information provided by DPR. For methyl bromide, DPR provides this information as suggested permit conditions. In 1993, DPR began developing new use practice restrictions for agricultural applications that would incorporate a one-day (24-hour) exposure level of 0.21 ppm for workers and public. The suggested permit conditions include equipment modifications, restrictions on work hours, limits on application rates, limits on acreage or volume treated, tarpaulin specifications, restricted entry requirements, enclosed space requirements, and establishment of buffer zones. A review of the restrictions on the use of methyl bromide was conducted in a report to the California legislature (DPR, 1996). Most of the permit conditions have been adopted as regulations (DPR, 2001a). The 2001 regulations also included a requirement of mandatory buffer zones for most applications. Additional protective measures were required when fumigation sites around schools, hospitals, and other “sensitive” sites, including a prohibition on fumigation when school is in session. A two-stage notification plan was devised for neighbors before fumigation. Additional restrictions and buffer zone requirements were determined to minimize the exposures of workers on nearby properties and property owners. DPR is now examining the potential for seasonal exposures by workers and person who live in the vicinity of recurring fumigations. Data from the air monitoring in 3 counties (Kern, Monterey, and Santa Cruz) showed high exposure levels in some areas (ARB, 2000 and 2001; DPR, 2001b[4]). DPR has placed methyl bromide into reevaluation and is requiring methyl bromide registrants to conduct ambient air quality monitoring in areas with highest seasonal use (DPR, 2001c).

II.C. TECHNICAL AND PRODUCT FORMULATIONS

In 2001, 54 methyl bromide-containing products were registered in California. The registrants of methyl bromide products are Ameribrom, Inc., Albemarle Corporation, Great Lakes Chemical Corporation, Soil Chemicals Corporation, Trical, and Shadow Mountain Products Corporation. The products are available as 100% methyl bromide and as mixtures with chloropicrin (range of 0.25% to 67% chloropicrin). Methyl bromide is used as a fumigant on raw and processed agricultural commodities, in structures, in soil, and on ornamentals.

[4] See Attachment H.

II.D. USAGE

There are two major types of methyl bromide fumigations: applications to an area of soil or applications to an enclosed volume (e.g., chamber, building). All applications to soil occur prior to planting the crop for control of a wide variety of pests. Most soil applications involve the injection of methyl bromide beneath the soil surface. Injection can either be shallow (12 inches or less) or deep (20 inches or more), depending on the crop to be planted. In many cases, but not all, the soil is covered with a plastic tarpaulin to retard methyl bromide off-gassing. For typical agricultural field applications, a tractor injects the methyl bromide through a set of chisels or shanks, and lays the tarpaulin all at the same time. Applications can either be to a flat field (broadcast application) or to a field with beds and furrows (bed application).

Applications to post-harvest commodities or other enclosed volumes are very different. The types of enclosures and their efficiency in retaining methyl bromide are quite varied. The more typical enclosures include chambers, transportation containers, tarpaulins, and buildings. Regardless of the enclosure, most applications follow a general three-step process: 1) introduction or injection of methyl bromide into the fumigated space—this step usually takes a few minutes; 2) a treatment or holding period—usually a few hours to a few days; 3) aeration of the fumigated space—also a few hours to a few days. The method of aeration can also be quite varied. Most chambers will have an elevated exhaust stack and release methyl bromide at a controlled rate, but tarpaulin applications are aerated simply by removing the tarpaulin.

From 1992-1999, about 14-18 million pounds of methyl bromide were used each year for soil, commodity, and structural fumigations in California (DPR, 2000a). In 2000, the reported pounds of pesticides used were reduced to 10.8 million pounds (DPR, 2000a). The major uses (% of total pounds used) in field fumigation were strawberry fields (39%), outdoor nursery uses (12%), and preplant soil fumigation (12%). The use of methyl bromide in structural fumigation has declined significantly to about 3% of total pounds used because of regulation that required extended aeration time before residents are permitted to reenter the homes.

II.E. ILLNESS REPORTS

Poisonings by inhalation exposure to methyl bromide have been reported as early as 1899 (von Oettingen, 1946). A review of the incidents published from 1939-1981 showed 115 incidences of fatalities and 843 incidences of non-fatal systemic or local injuries (Alexeeff and Kilgore, 1983). In California, illnesses associated with inhalation exposure to methyl bromide have been reported and are described in detail in Attachment F. Approximately 50% of the cases also involved another compound or compounds. In the work place, the most common cause of the illnesses was equipment failure. Exposure of the general population to methyl bromide was due primarily to drift from fumigated fields. Specific case studies and human epidemiological studies are presented in the **III.H. NEUROTOXICITY**.

II.F. PHYSICAL AND CHEMICAL PROPERTIES[5]

Chemical name:	bromomethane, monobromomethane
CAS Registry number:	74-83-9
Common name:	methyl bromide
Trade names:	Brom, Brom-O-Gas, M-B-R, Metabrom, Meth-O-Gas, Methyl Bromide, Pic-Brom, Terr-O-Gas, Tri-Brom, Tri-Con, Tri-Pan.
Molecular formula:	CH_3Br
Molecular weight:	94.95 g/mole
Chemical structure:	CH_3-Br
Physical appearance:	colorless gas, usually odorless; sweetish, chloroform-like odor at high concentrations (odor threshold at 80 mg/m^3 or 20.6 ppm); burning taste. It is nonflammable in air but does burn in oxygen.
Solubility:	1.75 g/100 g in water (20°C, 748 mm), forms a crystalline hydrate, $CH_3Br \cdot 20\ H_2O$, below 4°C; freely soluble in alcohol, chloroform, ether, carbon disulfide, carbon tetrachloride, benzene.
Boiling point:	3.56°C
Melting point:	-93.66°C
Octanol/Water partition coefficient:	log P=1.19 (15.5:1 octanol:water)
Vapor pressure:	1420 mm Hg (20°C), 2600 mm Hg (40°C)
Specific gravity:	3.3 g/ml (gas), 1.7 g/ml (liquid)
Conversion factor:	1 ppm = 3.89 mg/m^3 at 25°C

[5] Farm Chemical Handbook, 1998; The Merck Index, 1989; U.S. EPA, 1986b.

II.G. ENVIRONMENTAL FATE

Summary: Methyl bromide is degraded in the environment. The rate of hydrolysis was enhanced by elevated temperature, ultraviolet irradiation, aerobic conditions, and high organic matter in the soil. Once applied to the soil, methyl bromide volatilized into the air or adsorbed onto soil particles. Because of degradation, methyl bromide residues were not detected in the groundwater or commodities grown on fumigated soil. Residues were found in treated commodities after post-harvest fumigation.

II.G.1. Hydrolysis

Methyl bromide hydrolyzed to bromide in water (WIL, 1985a). The hydrolytic half-life was estimated to be 6 days for pH 9 at 35°C to 49 days for pH 7 at 25°C. There was leakage of methyl bromide from the flasks used in the experiments.

II.G.2. Photolysis or Photodegradation

Methyl bromide in solution (1.7×10^{-2} M) completely hydrolyzed to methanol, bromide, and hydrogen ion when irradiated at 254 nm for 40 days (Castro and Belser, 1981). The photolysis rate constant was 2×10^{-6} sec^{-1}, 6.6-fold higher than without irradiation. However, experiments with incubation in the dark and in sterilized water were not performed.

In the upper stratosphere, methyl bromide was photo-dissociated, lost by diffusion, and reacted with hydroxyl radical (WHO, 1995). The products of these reactions were carbon dioxide, carbon monoxide, and bromide species. Photodegradation of methyl bromide was rapid in moist air (Gennari *et al.*, 1995). The half-lives were 22 minutes with irradiation at 250-420 nm and 15 mg/L moisture to 326 hours with irradiation at 366-750 nm and 15 mg/L moisture.

II.G.3. Microbial Degradation

There was no difference in the methyl bromide degradation half-lives between sterilized and unsterilized soils because methyl bromide decreased the microbial activity in both soils (Radian Corp., 1988). However, the half-lives under aerobic conditions were shorter than those for anaerobic conditions. The degradation in clay loam, with a higher organic content, was faster than in sandy loam. The average half-lives for sandy loam and clay loam soils were 35 and 3.8 hours, 47 and 2.5 hours, 144 and 39 hours, and 80 and 34 hours, under aerobic/ nonsterile, aerobic/sterile, anaerobic/nonsterile, and anaerobic/sterile conditions, respectively.

II.G.4. Mobility (Soil, Ground Water, Air, Plants)

II.G.4.a. Soil

The mobility of methyl bromide in soil, as with other soil fumigants, depends on many factors: chemical and adsorptive characteristics of the fumigant, temperature, moisture, organic matter, soil texture, and soil profile variability (Munnecke and Van Gundy, 1979; Kolbezen *et al.*, 1974; Abdalla *et al.*, 1974). The following section is a summary of some studies.

Thirty-two days after exposure to 200,000 ppm in the air, the soil contained less than 1.5 ppm methyl bromide (Radian Corp., 1988). This level was decreased by 10-fold after the soil was purged with nitrogen as methyl bromide was loosely associated with the soil. The proposed reaction of methyl bromide in the soil was: $CH_3Br + O_2 \rightarrow HBr + H_2O + CO$, then $2CO + O_2 \rightarrow 2CO_2$, with CO=carbon monoxide and CO_2=carbon dioxide.

Under laboratory conditions, volatilization was the major route of dissipation from the soil (WIL, 1985b). The initial loss rate was 82.6 *u*g/cm^2/hour and the steady state rate was 8.8 *u*g/cm^2/hour. Under similar conditions, the rate of loss for chloropicrin was much slower with a steady state rate of 1.8 *u*g/cm^2/hour.

Methyl bromide decomposed to bromide in all soil types (sand, peat, and loam) tested (Brown and Rolston, 1980). Decomposition was greatest in peat soil containing the most organic matter as the methyl group was transferred to the carboxyl groups and – and S-containing groups of the amino acids and proteins of soil organic matter. In loam soil, the decomposition reaction was first order depending on the air concentration. The retention of methyl bromide in soil depended on soil water content. In dry sand, the adsorption and desorption rates of methyl bromide were similar. In moist sand, the desorption was slower (30% of adsorption) than adsorption.

Methyl bromide in water adsorbed to Canfield silt loam, Holly silt loam, and Wooster silt loam more than agricultural sand (WIL, 1986). The methyl bromide concentrations were 18 ppm in Canfield, 17 ppm in Holly, and 14 ppm in Wooster loam soils; but only 6 ppm was in sand. When the treated soil was mixed with water, 89 to 97% of the adsorbed methyl bromide were released from the soil and the equilibrium was reached in 24 hours.

Methyl bromide concentration and half-lives in Reiff (fine sandy loam) and Yolo loam were similar after preplant injection (6-8 inches deep) into the soil and then tarped, (MBIP, 1986). The highest concentration was at the level (1 foot) of injection. The dissipation half-life was the fastest at 1 foot (0.9-1.2 days) and the slowest at 3 feet deep (4.1 to 5.9 days). With deep injection of 18-24 inches and nontarped preplant injection, the dissipation half-lives ranged from 2.8 days at 1 foot to 9.6 days at 8 feet deep. When methyl bromide-treated soil was drenched with water and steamed upon removal of the tarp, methyl bromide was detected as far as 2 feet below the surface. The dissipation half-lives ranged from 2.5 to 3.0 days for the application rate of 1 lb/100 square feet, and 2.5 to 11.0 days for 2 lb/100 square feet.

Methyl bromide was retained after application beneath concrete slabs (McKenry and Secara, 1990). Methyl bromide (128 kg) was introduced into the ground via holes drilled through the floor and then the floor was tarped for 4 days. After treatment, the highest concentration was approximately 9,000 ppm on day 2 at 30 cm from the house and 90 cm deep underneath the floor. The concentration in the soil declined as the distance from the injection point was increased; however, even at 150 cm away, the concentration was as high as 5,700 ppm on day 3. The use of an air compressor to deliver air to the soil air space on day 15 enhanced the dissipation of methyl bromide. The concentration of methyl bromide at 15 cm beneath the slab remained below 21 ppm and averaged 8 ppm one week after the final air compressor treatment. With continuous aeration, the methyl bromide concentration in the open portion of the house did not exceed 88 ppb. The ambient concentrations of the backyard and neighboring houses were

below 6 ppb during treatment and aeration.

II.G.4.b. Ground Water

Methyl bromide was not detected (detection limit of 1 ppb) in ground water samples from fields (muck and sandy type soils) in Florida (Pickrell *et al.*, 1985) and wells in Florida and California (Golder Associates, Inc. 1985a and b). The wells in California had a history of more than 10 years of methyl bromide use with the last fumigation 5 to 17 months before the study (Golder Associates, Inc. 1985b).

II.G.4.c. Air

The major sources of bromide and methyl bromide in the air are marine aerosols and natural marine biological processes, respectively (Lovelock, 1975; Wofsy *et al.*, 1975). Methyl bromide from fumigation uses was estimated at 25% of the total emissions (natural and anthropogenic) (Watson *et al.*, 1992). A minor source of methyl bromide is the exhaust from cars that use leaded gasoline (Harsch and Rasmussen, 1977). Measurements of methyl bromide over the Atlantic Ocean showed average concentrations of 15.4±1.9 parts per trillion (ppt) and 10.6±0.9 ppt for the Northern and Southern Hemispheres, respectively (Penkett *et al.*, 1985). The calculated total lifetime in the atmosphere was 1.16 years (Lobert *et al.*, 1995). In a survey conducted in 1979, the mean levels of methyl bromide in the ambient air were 244 ppt in Los Angeles, CA; 66.8 ppt in Phoenix, AZ; and 54.7 ppt in Oakland, CA (Singh *et al.*, 1981). Worldwide environmental levels are in the review by WHO (1995).

Methyl bromide degradation in the air involved reactions with hydroxyl radicals and ozone. Based on an estimated hydroxyl radical concentration of 2×10^6 /cm^3 in the daytime, the estimated residence time in the air was 289 days with a daily rate of loss of 0.4% (Singh *et al.*, 1981). In the winter months when hydroxyl radical concentration could be lowered, the residence time would increase. The bromide from the degradation reactions reacted with ozone by the following reaction (Wofsy *et al.*, 1975; Watson *et al.*, 1992).

$Br^- + O_3 \rightarrow BrO^- + O_2$, with net reaction of $2O_3 \rightarrow 3O_2$.

The release of methyl bromide after structural fumigation was monitored in close proximity and nearby fumigated homes (Gibbons *et al.*, 1996 a and b). During fumigation, air levels ranged from less than 0.019 to 1.495 ppm when monitored at 10 feet from the fumigated houses. At the neighboring houses, the air levels ranged from 0.012 ppm (detection limit) to 0.351 ppm. During aeration, the concentrations inside the houses at 50 and 100 feet downwind from the fumigated house depended on the aeration method and time of sampling. Compared to the Standard Method, the Pest Control Operators of California Aeration Method resulted in lower concentrations (7.5 ppm versus 13.6 ppm) at the 10-feet distance after 1 hour of aeration, but not those after 24-hour aeration, or at greater distances.

Liscombe, *et al.* (1995 and 1996) tested alternative tarping and aeration methods to mitigate methyl bromide air concentrations from structural fumigations. During treatment, air concentrations ranged from 0.035 to 1.08 ppm five feet from the fumigated structure, depending on the method of tarping. During aeration, air concentrations ranged from 0.021 to 0.11 ppm.

Adding a second tarpaulin and aerating through an elevated stack were the most effective methods for reducing air concentrations.

Prior to 1992, limited monitoring of field fumigations was conducted. Methyl bromide levels in the air after tarpless fumigation of soil were determined in four farms (Soil Chemicals Corp., 1990). The shanks were placed 10 to 12 inches deep into the soil and the results are summarized below:

Farms	Sampling site	Time	Methyl bromide level
Belridge	60 ft downwind	several hours after fumigation	<30 ppb to 114 ppb
Kirschenman	150 ft downwind	0-11 hours after fumigation	<30 ppb (all times)
Major	200 ft downwind	during fumigation	<30 ppb to 211 ppb
Firini	in field	during fumigation	126 ppb
Firini	200 ft downwind	during fumigation	<30 ppb

In a monitoring study conducted by the Air Resources Board, Cal/EPA, air samples were collected on 3 off-sites close to strawberry fields and 4 sites in the nearby towns before and after application of methyl bromide (Seiber *et al.*, 1987). The fumigated field was tarped for 4 days. Methyl bromide levels were all below the MDL (1.1 ppb) for samples of ambient air in nearby towns. Methyl bromide was found in 3 off-sites (275, 76, and 175 meters from the field). The maximum levels (210-900 ppb) were detected on the day after application with a rapid decline on the next day. The highest average air concentration for an approximately 24-hour period was 450 ppb for site B, based on three 3-hour measurements. This level was used in the 1992 DPR Preliminary Risk Assessment (Attachment A).

Beginning in 1992, DPR, methyl bromide registrants, and academic researchers began more comprehensive monitoring of field and commodity fumigations. Details of the studies and the results are presented in Appendices F and H. The results were used to develop buffer zones for these uses.

II.G.5. Plant Residues/Metabolism

Methyl bromide residue in the food is generally analyzed by head-space gas chromatography (King *et al.*, 1981). This method requires the blending of macerated commodities in water. After the slurry is allowed to stand, methyl bromide which partitioned into the headspace is measured. The major uncertainty of this method is the time required for partitioning to reach an equilibrium that depends on the commodity composition and extent of methyl bromide interaction with endogenous components. The review of studies in the following section does not include some residue data submitted to DPR as part of the methyl bromide dietary risk characterization.

II.G.5.a. Field Fumigation

Methyl bromide *per se* is generally not found in commodities grown on soil pretreated with methyl bromide because of its dissipation and degradation (MBIP, 1988a; Trical, Inc., 1985, 1990, and 1991; WIL, 1984). When methyl bromide was injected into the soil 15 days before planting and the field was tarped for 6 days, low levels of methyl bromide were found (Trical, Inc., 1985). The sampled crops and levels were: lettuce (< 3 ppb-29 ppb), turnip roots (< 23

ppb-644 ppb), broccoli (< 250 ppb-1452 ppb), carrots (<16 ppb), green tomatoes (< 16 ppb), green beans (< 10 ppb). With cucumbers, two of the four samples contained residues at 5 and 34 ppb. In turnip leaves, methyl bromide levels ranged from < 9 ppb to 334 ppb; the control samples were all < 9 ppb. Matrix interference in the analysis was especially notable in broccoli and turnip roots. The levels of methyl bromide in two processed foods, tomatoes and dried beans, were below detection limits (10 ppb, and 6 ppb, respectively). Residues were also not detected in potatoes (< 5 ppb) and carrots in other studies (Trical, Inc., 1990 and 1991).

In a survey of methyl bromide residues after either broadcast application or bed treatment fumigation, 4 samples from each crop from 9 states (California, Florida, Oregon, Washington, Texas, Michigan, Arizona, Idaho, Hawaii, Wisconsin, and North Carolina) were analyzed (MBIP, 1988a). Most of the samples were collected in California. The crop groups and representative crops sampled were: root and tuber (carrot, potato, radish, and sugar beet); bulb vegetables (green onion, large bulb onion, small bulb onion, and garlic); leafy vegetables (head lettuce, leaf lettuce, celery, and spinach); Brassica vegetables (broccoli, cabbage, cauliflower, and mustard greens); legume vegetables (bush bean, green bean, soybean, succulent pea, and dry pea); fruiting vegetables (tomato, and pepper); cucurbit vegetables (cucumber, zucchini, watermelon, cantaloupe, and summer squash); citrus fruits (orange and grapefruit); pome fruits (apple); small fruits (raspberry, blueberry and strawberry); non-grass animal feed (alfalfa and clover); herbs and spices (basil, chives, dill, and marjoram); and miscellaneous (asparagus, ginger, grape, peanut, pineapple, corn, tobacco, and okra).

Almost all the samples contained residue levels below detection limits (ranged between 5 to 10 ppb). For mustard greens, the residue levels were 20.20 to 29.9 ppb (mean=24.9 ppb) for samples from California. In the Florida trial of cabbage, two of the four samples were 13.8 and 15.18 ppb and the other two were below the MDL (10 ppb). Since most of the samples did not contain residues, the levels above the MDL could be false positives due to dimethyl disulfide or other sulfur compounds. Bromide levels were determined in some crops and in general, were not indicative of methyl bromide application rates. For example, the mean bromide level in treated celery (442 ppm) was 4 times that of control (105 ppm). For pineapple, strawberry, and asparagus, bromide levels in the control and treated samples were similar (20 to 40 ppm).

II.G.5.b. Post-harvest Fumigation

The use of methyl bromide as a post-harvest fumigant on raw agricultural commodities and processed foods resulted in detectable levels of residues (Attachment C). Only residue data with adequate information of fumigation conditions and analysis method are included in Attachment C. In commercial practices, the fumigation condition is dictated by the pests of concern and the potential phytotoxicity by methyl bromide. In general, fresh fruits and vegetables are fumigated at short intervals (2 hours), and then stored at cool temperature.

The residue levels in fumigated foods were dependent on the nature of the commodity; load factor (volume of commodity to chamber size); application rate, temperature, frequency, and duration; as well as aeration and storage conditions. The half-lives of methyl bromide in fruits and vegetables were shorter than those for nuts and dried fruits. With cherries, there was an inverse relationship between load factor and initial residue levels such that an increase in the load factor from 1.6% to 32.0% resulted in lower residue levels (Sell *et al.*, 1988). Consequently,

a shorter aeration period was needed to achieve a certain residue level. In addition, an increase in pulp temperature enhanced the desorption of methyl bromide from the cherries. For example, the aeration period required to obtain 1 ppm methyl bromide remaining on the cherries was reduced from 18 hours to 9 hours when the pulp temperature was increased from 7°C to 27°C.

Likewise, an increase in temperature during fumigation or during aeration or storage resulted in the decrease of half-lives of methyl bromide in blueberries, walnuts, and strawberries (Attachment C). While an increase of the application rate from 2 to 4 lbs/1000 ft^3 (plum, nectarine, or peach) or a doubling of exposure duration (avocado, peach, or pear) resulted in higher initial residue levels, there was no significant change in the half-lives. However, a 4-fold increase in an application rate (mango) resulted in an increase of both the initial residue levels and half-life.

Aeration lowered methyl bromide residues in fumigated strawberries (MBIP, 1984b). After 45 min, 1 hour, 2 hours, and 3 hours of aeration, the methyl bromide levels were 9.0 ppm, 7.0 ppm, 5.4 ppm, and 140 ppb, respectively. Samples which had been aerated for only 45 minutes before precooling contained 7.1 ppm of methyl bromide. The level then declined to 2.1 ppm and 1.6 ppb after 12 and 24 hours, respectively. Samples with 3 hours of aeration contained only 20-30 ppb after 2-3 hours at 34°F (1°C). No methyl bromide (MDL not specified) was detected in fumigated strawberries stored at 70°F (21°C) instead of 34°F (1°C). For asparagus, the mean residue level decreased from 2.14 ppm after fumigation to 0.016 ppm after 24 hours of aeration (Fieser and Conrath, 1993).

Because of the higher lipid content, the half-lives of methyl bromide in nuts (almonds, pistachio nut, and walnut) were longer than those for fruits (Attachment C). Methyl bromide absorbed into the almond shell and the kernel by dissolution of methyl bromide in the oil particles (Hartsell *et al.*, 1983). Some residues were released during aeration while others methylated amino acids or phenolic materials such as tannin and lignin. The shell generally contained higher levels of bromide and methyl bromide residues than the kernel. The highest bromide level was found in the Mission variety of almonds with the highest lignin and tannin contents, while lower levels were found in the Mercedes, Carmels, and Nonpareils varieties. Increase of temperature resulted in increased residues in the shell and kernels. During aeration, methyl bromide evaporated more rapidly from the shell than the kernel, but reached a similar concentration (< 2.5 ppm) in both compartments by about 50 hours.

Methyl bromide deposition in avocados was also related to the fat content (Singh *et al.*, 1982). The Fuerte variety absorbed 57% more methyl bromide and formed 22% more bromide than the Haas variety. Methyl bromide (21-36% conversion in Fuerte and 56-70% in Haas) was converted to bromide during storage.

Processing of fumigated grains reduced methyl bromide levels in the final product (MBIP, 1984a and 1988b; CMA, 1984). When wheat was processed to wheat flour, the levels ranged from below the detection limit (<1 ppb) to 2 ppb. For corn, grinding and baking at 350°C for 1 hour reduced the fumigated level (9.4 ppm) to 6.4 ppm and <0.01 ppm, respectively (MBIP, 1984a). Methyl bromide level in rice decreased from 5.2 ppm to < 0.01 ppm after 20 minutes of simmering. All flour and bakery mix samples had < 0.03 ppm methyl bromide.

Methyl bromide residues were higher (as much as 2-fold) in packaged dried fruits (dates, apricots, prunes) than in bulk form, except raisins (Attachment C). Because packaging provided limited off-gassing, the half-lives of methyl bromide in these commodities were also longer than those for bulk forms.

The dissipation half-lives provide only a qualitative estimate of the potential exposure by the consumers since multiple fumigations can occur to prevent reinfestation during processing and storage, either as bulk or packaged goods. A survey of nuts at the retail level showed methyl bromide levels ranged from 10 ppb to 3.7 ppm in 8 of 75 samples (Lindsay, 1985).

The U.S. Food and Drug Administration (FDA) collected samples of processed nuts, dried fruits, dried beans, and rice from the marketplace and analyzed them for methyl bromide (FDA, 1990-1991). Of the 1132 nut samples, only 2 pistachios samples contained detectable levels of residues (0.09 ppm and 0.03 ppm). Residues were not detected in 107 samples of rice, 347 samples of dried fruits, and 173 samples of dried beans; the MDL was 0.02 ppm (Ford *et al.*, 1992).

In a field-trial study, selected commodities were fumigated with methyl bromide at rates which ranged from 2-5 pounds/ 1000 ft^3 for 2 to 24 hours according to the label uses (DFA, 1985; MBIP, 1985a). Methyl bromide residue levels were determined after 1, 3, or 7 days of aeration. The crop groups and selected commodities included: pome fruits (apple, pear), tree fruits (almond, walnut, and pistachios), root and tuber vegetables (carrot, potato, and sugar beet), legume vegetables (beans, peas, and soy beans), citrus fruits (orange, lemon, grapefruit), stone fruits (peach, plum), cereal grains (corn, rice, wheat), bulb vegetables (onion, garlic), fruiting vegetables (tomato, pepper), small fruits and berries (blackberry, blueberry, grape, and strawberry), herbs and spices (basil, chives, dill, and sage), leafy vegetables (broccoli and cabbage), cucurbits (cucumber, melon, and summer squash), processed (wheat, corn, rice), and miscellaneous (cocoa beans, dried fruits, and candy).

In wheat grown in sand containing ^{35}S-labeled sulfate and subsequently fumigated, the gluten or protein fraction contained N-methyl derivatives, dimethylsulfonium derivatives, as well as methyoxy- and methythio- derivatives (Winteringham *et al.*, 1955). Further study with fumigated wheat flour showed that methyl bromide methylated the basic nitrogen residues (Bridges, 1955). The histidine residue was the primary site of methylation resulting in the formation of 1-methylhistidine, 3-methylhistidine and 1,3-dimethylhistidine (Bridges, 1955). Studies with diets containing high levels of methylated histidines (0.36% of the diet) showed that these residues are not available for nutritional use resulting in weight loss in mice (Friedman and Gumbmann, 1979).

II.G.5.c. Structural Fumigation

Foods remaining in the house during fumigation may also acquire methyl bromide residues (Scheffrahn *et al.*, 1992). Packaged foods (unopened or reclosed) were fumigated with methyl bromide at approximately maximum labeled rates. Of the 23 food items, the highest residues were found in fatty commodities such as peanut butter (106 ppm) and margarine (151 ppm). Residue levels were below the detection limit in foods unopened with the factory seal intact or vacuum-packed.

III. TOXICOLOGY PROFILE

Pharmacokinetic and toxicity studies of methyl bromide are summarized in this section. Acceptability of the studies (except genotoxicity studies) by DPR, where noted, was based on the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies was based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). The toxicology summary for studies reviewed for The Birth Defect Prevention Act of 1984 (SB 950) is included in Attachment D. In the toxicity studies, the no-effect levels may be expressed as NOELs or no-observed adverse effect levels (NOAELs). For the purpose of this document, endpoints under either designation are considered relevant for hazard identification.

Summary tables for selected toxicity studies considered for critical no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) are presented in Tables 5, 7, and 14 for acute, subchronic, and chronic exposures, respectively. Unless stated, concentrations are as measured concentrations from the studies. For comparison of toxicity between studies in these tables, the NOELs were also presented in terms of human equivalent NOEL. This human equivalent NOEL takes into consideration the air concentration, duration of exposure, and intake rate (respiration rate for inhalation exposure) differences between experimental animals and humans (adult and child) using equations in Attachment G. Since the experiments were conducted for various durations, the human equivalent NOEL is calculated on a per day basis to allow comparisons between studies. This approach follows the dose calculation methods outlined in the 1992 U.S. EPA Exposure Assessment guidelines, where the potential dose is a function of the concentration and intake rate (U.S. EPA, 1992c). It has generally been used for dietary exposure studies where the no-effect level is expressed as the dose (for example as mg/kg/day) accounted for consumption rate and duration of exposure, instead of concentration in the diet. Since the equivalent NOEL for children is lower than that for adults, only the children equivalents NOELs are presented in the summary tables. The only exceptions are the NOELs for developmental or reproductive toxicity studies since the endpoints are applicable only to adult exposures.

The internal doses for inhalation studies were assumed to be due to inhalation only. The inhalation pharmacokinetic studies were conducted with nose-only exposure while the toxicity studies (except where noted) were done with whole-body exposures. For laboratory animals in whole-body inhalation exposure studies, additional exposure was possible from oral ingestion due to licking of the fur and by dermal absorption. The internal dose from whole-body exposure may be higher than that calculated based only on the air concentration and respiration rates.

III.A. PHARMACOKINETICS

Summary: After inhalation, intraperitoneal, or oral administrations, methyl bromide was rapidly absorbed and radioactivity (^{14}C) was distributed to all tissues. With inhalation exposure, the percentages of the administered doses absorbed were similar in several species; they were 48% in the rat, 40% in the dog, and 52 to 55% in humans. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure. With oral and intraperitoneal administration to rats, more than 90% of the dose was absorbed with the highest radioactivity levels measured in the liver, kidneys, and testes. Methyl bromide was extensively

biotransformed into unidentified products and carbon dioxide. In the rat, within 1 hour after inhalation exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. In humans, both methyl bromide and inorganic bromide were detected in the tissues 5 hours after a lethal dose exposure. The primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for oral exposure. Carbon dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity in the exhaled air. After oral administration, biliary metabolites of methyl bromide were reabsorbed from the gut.

III.A.1. Absorption

Fischer-344 rats were exposed to methyl bromide (^{14}C, >98% pure; nominal concentrations of 1.6, 9.0, 170, or 310 ppm) by nose only inhalation for 6 hours (Medinsky *et al.*, 1985). For 1.6, 9.0, and 170 ppm, the percentages of the absorbed dose (the ratio of radioactivity in the whole body homogenate after 6 hours to the amount inhaled x 100%) were 48%, 48%, and 38%, respectively. At 310 ppm, there were significant ($p \leq 0.05$) decreases in the tidal and minute volumes resulting in the absorption of only 27% of the total dose. At 66 hours after exposure, 17 to 26% of the total absorbed radioactivity remained in the body.

In beagle dogs, the calculated steady-state fractional, systemic uptake of the total inhaled methyl bromide (^{14}C, >98% pure, 174 to 361 ppb) was 39.5% after exposure for 3 hours by nose only, (Raabe, 1986). After the three-hour exposure, the blood concentration was 1.6% of the total amount inhaled and it declined to 1.2% at 117 hours after exposure.

In a human study, four volunteers (2 male and 2 female adults) were exposed to methyl bromide (^{14}C, >98% pure, 18 ± 6 ppb) for 2 hours by nose breathing and by mouth breathing (Raabe, 1988). Each subject was equipped with a two-stage demand regulator-based inhalation system that separated inhaled and exhaled air. The calculated steady-state, fractional systemic uptake of the total inhaled methyl bromide during nasal breathing and mouth breathing were 55.4% and 52.1%, respectively.

For oral and intraperitoneal administration in rats, the absorption was >90% when determined 72 hours after exposure (Medinsky *et al.*, 1984).

III.A.2. Distribution

After inhalation exposure to methyl bromide, radioactivity was found in the liver, kidneys, adrenal glands, lungs, thymus, brain, testes, and nasal turbinates in the rat (Medinsky *et al.*, 1985; Bond *et al.*, 1985; Jaskot *et al.*, 1988). The peak radioactivity levels in the tissues occurred immediately after exposure. The tissues with high radioactivity included the lungs, liver, and the nasal turbinates. In the study by Jaskot *et al.* (1988), the half-lives of tissue radioactivity were 2.71 hours (lung), 1.58 hours (liver), 0.58 hours (kidney), 1.37 hour (spleen), 6.54 hours (brain), and 5.29 hours (testes). In another study, the half-life of the radioactivity in the liver was 33 hours, while the half-lives were shorter in blood (7.7 hours), and in testes, small intestine, and brain (6 hours) (Bond *et al.*, 1985).

In a poisoning case, a man ingested and inhaled an unknown amount of methyl bromide

for approximately 1.5 hours and died 4 hours later (Michalodimitrakis *et al.*, 1997). Tissues were sampled 1 hour after death during the autopsy. Except for the spleen, methyl bromide was found in all tissues. The methyl bromide levels were: subclavian blood (3.8 *u*g/ml), brain (3.5 *u*g/g), adrenal gland (3.4 *u*g/g), peripheral blood (3.3 *u*g/ml), lung (2.9 *u*g/g), testis (2.8 *u*g/g), kidney (2.6 *u*g/g), liver (1.9 *u*g/g), bile (1.2 *u*g/g), and epididymis (1.2 *u*g/g). The inorganic bromide levels were: subclavian blood (530 *u*g/mL), brain (30 *u*g/mL), peripheral blood (480 *u*g/ml), lung (410 *u*g/g), kidney (310 *u*g/kg), and bile and epididymis (none).

After intraperitoneal or oral administration of methyl bromide (^{14}C, >98% pure, 250 *u*mol/kg or 23.7 mg/kg), the radioactivity levels (in decreasing order) in Fischer-344 rats tissues were: liver > kidney, testes > lung, heart, stomach > spleen (Medinsky *et al.*, 1984).

III.A.3. Biotransformation/Excretion

In rats exposed to methyl bromide by inhalation, 47 to 50% of the absorbed dose was exhaled as CO_2 and 0.4 to 4% as methyl bromide (Medinsky *et al.*, 1985). Excretion in the exhaled air was biphasic with a half-life of 4.1 hours in the initial phase and 17 hours in the second phase. Approximately 20% of the absorbed radioactivity was excreted in the urine, while only about 1% was found in the feces. The urinary half-life for radioactivity was 9.9 hours.

In another inhalation study with rats, methyl bromide was rapidly biotransformed and readily excreted in rats after inhalation exposure (Bond *et al.*, 1985). In all tissues examined, over 90% of the radioactivity was metabolites. The elimination half-life of radioactivity from the tissues was 1.5 to 8 hours. Nearly 75% of the absorbed dose was excreted by 65 hours with exhalation as the primary route. The excretion of $^{14}CO_2$ in the exhaled air was biphasic with the initial half-life at 3.9 hours, and a later half-life of 11.4 hours. The half-lives of radioactivity were 9.6 hours and 16.1 hours in the urine and feces, respectively. The percentages of the absorbed dose excreted in the expired air as CO_2, in the expired air as methyl bromide, in the urine, feces, and retained in the body were 47%, 1%, 23%, 2%, and 28%, respectively. A similar excretion pattern was reported by Jaskot *et al.* (1988).

In dogs, the excretion of radioactivity was 1% (total inhaled) in the urine, 0.04% in the feces, and 9.86% in the lungs when measured 0 to 21 hours after exposure to methyl bromide (Raabe, 1986). At 69 hours after exposure, 5.7% and 0.7% of the total amount inhaled were excreted in the urine and feces (Raabe, 1986). The estimated total clearance half-life was 41 hours.

In humans, the amount exhaled as $^{14}CO_2$ ranged from 0.2 to 1.0% of the dose for mouth breathing, and 0.2 to 0.4% of the dose for nose breathing exposure when measured at the end of 2 hours of exposure and after 0.5 hour for clearance (Raabe, 1988). Radioactivity levels excreted in the urine ranged from 0.08 to 0.24% for mouth breathing, and from non-detected to 0.32% for nose breathing. The determination of urinary clearance was complicated by the variability in the volume. The net body retention for both exposure routes was 51.1% with a clearance half-life of 72 hours based on the amounts in the exhaled air and in the urine at 0.5 hour after inhalation exposure.

In rats after oral exposure, the distribution (as % of an absorbed dose) was 32% as

$^{14}CO_2$ and 4% as intact methyl bromide in exhaled air, 43% in the urine, and 14% in the carcass at 72 hours after exposure to methyl bromide (^{14}C, >98% pure, 250 *u*mol/kg or 23.7 mg/kg) (Medinsky *et al.*, 1984). Only 2% of the dose was found in the feces. In cannulated rats, biliary excretion was a major pathway as 46% of the dose was found in the bile and only 12% and 7% in the exhaled CO_2 and urine, respectively, at 24 hours after dosing.

With intraperitoneal administration, the cumulative percentages of the doses in rats measured after 72 hours were: 45% as $^{14}CO_2$ and 20% as intact methyl bromide in exhaled air, 16% in the urine, 1% in the feces, and 17% in the carcass (Medinsky *et al.*, 1984).

III.B. ACUTE TOXICITY

Summary: Methyl bromide is a Toxicity Category I compound because of its acute inhalation toxicity (Federal Register, 1991b)[6]. Severe irritation to eyes, skin, and mucous membranes occur after acute exposure; therefore, acute oral, ocular and dermal studies are not required for registration. Neurotoxicity has been observed in humans and laboratory animals after inhalation exposure to methyl bromide with severity depending on the dose and duration of exposure. In humans exposed to high concentrations, neurological effects included ataxia, convulsion, and tremors. The nonlethal effects observed in laboratory animals included changes in brain catecholamines and tyrosine hydroxylase activity, tissue degeneration (nasal, brain, and adrenal glands), and neurotoxicity (ataxia and paralysis). Signs of oral toxicity in the dog included prostration, increased heart rates, lesions in multiple organs including the stomach and brain, hypoactivity, hypothermia, and death. Human dermal exposure resulted in skin lesions. The acute lethal toxicity of methyl bromide has been reviewed (Sayers *et al.*, 1929; Irish *et al.*, 1940; Alexeeff and Kilgore, 1983 and 1985; WHO, 1995). Studies considered for risk assessment are summarized in Table 5. NOELs and LOELs were determined only for those studies with adequate descriptions of the experimental protocol and results.

III.B.1. Inhalation - Rat

The first comprehensive study on the acute toxicity of methyl bromide in rats was conducted by Irish *et al.* (1940). Rats (strain not specified) were exposed to methyl bromide (99% pure, nominal concentrations of 0.42 to 50 mg/L or 100 to 13,000 ppm) continuously by inhalation, and the acute toxicity was determined. The lethal concentrations and exposure durations which resulted in 100% mortality rate are listed in Table 1. At 260 ppm for 20 hours, rats were excitable and jumped when stimulated. At concentrations < 2,600 ppm, they showed roughening of the fur, hunching of the back, drowsiness, heavy breathing, and occasionally lacrimation. After prolonged exposure, there were kidney damage, lung congestion and edema, and bronchopneumonia leading to death.

Fischer-344 rats were exposed to methyl bromide (99.9% pure; nominal concentrations of 0, 90, 175, 250, or 325 ppm) for 6 hours per day for 5 days (Hurtt *et al.*, 1987). At 325 ppm, severe tissue degeneration in the nasal cavity, brain (cerebellar and cerebral), liver, and adrenal glands as well as minor alteration in testicular histology (delayed spermiation) were observed. Three of seven rats in the 325 ppm group died after 3 exposures. In addition, diarrhea, hemoglobinuria, ataxia, tremors and convulsions occurred in these animals (325 ppm). Ataxia and diarrhea were also observed in the 250 ppm treated animals. No death or tremors were observed in animals at this and lower concentrations. The degeneration in the nasal cavity and other tissues was concentration dependent. There was partial or complete destruction of the olfactory epithelium in the 325 and 250 ppm groups. At 175 ppm, there was moderate degeneration of the cerebellum, adrenal glands, and nasal cavity. The NOEL was 90 ppm.

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[6] The criteria for Toxicity Category I include an inhalation LD_{50} of less than or equal to 0.05 mg/L, and fatal if swallowed, inhaled, or absorbed through the skin.

Table 1. The acute lethal toxicity of technical methyl bromide.

Species	Gender	Concentration ppm	Dosage mg/kg	Reference[a]
Oral LD_{50}				
Rat	M		214	1
Rat	M		104-133	2
Subcutaneous LD_{50}				
Rat	M		135	3
Inhalation LC_{100}				
Rat (6 min)	-[b]	13000		4
Rat (24 min)	-[b]	5200		4
Rat (42 min)	-[b]	2600		4
Rat (4 hr)	M	900		5
Rat (6 hr)	-[b]	520		4
Rat (26 hr)	-[b]	220		4
Rabbit (30 min)	-[b]	13000		4
Rabbit (1.4 hr)	-[b]	5200		4
Rabbit (11 hr)	-[b]	520		4
Rabbit (24 hr)	-[b]	260		4
Rabbit (32 hr)	-[b]	220		4
Guinea Pig (15 min)	-[b]	50000		6
Guinea Pig (1.5 hr)	-[b]	6950		6
Guinea Pig (3 hr)	-[b]	2290		6
Guinea Pig (8 hr)	-[b]	490		6
Inhalation LC_{50}				
Rat (15 min)	-[b]	5480		7
Rat (30 min)	-[b]	2700		8
Rat (4 hr)	M	780		5
Rat (8 hr)	M	310		8
Mouse (1 hr)	M	1200		9
Guinea Pig (5 hr)	-[b]	310		6
Lethality				
Human (5.5-7.5 hrs)[c]	M	8160		10
Human-adult (2 hr)[d]	M	60000		11

[a/] References: 1. Danse *et al.*, 1984; 2. Kiplinger, 1994; 3. Tanaka *et al.*, 1988; 4. Irish *et al.*, 1940; 5. Kato *et al.*, 1986; 6. Sayers *et al.*, 1929; 7. AmeriBrom, Inc. 1983; 8. Honma *et al.*, 1985; 9. Alexeeff and Kilgore, 1985; 10. Miller, 1943; 11. Wyers, 1945.

[b/] Gender was not specified in the study.

[c/] This man was found in convulsions in a refrigerator car fumigated with methyl bromide 5.5 to 7.5 hours earlier. He was provided with life support but died 80 hours after removal from the car.

[d/] This worker used methyl bromide to extinguish a fire and then continued to work for 2 hours. He was hospitalized and died one hour later.

In a subsequent study, Fischer-344 rats were exposed to methyl bromide (99.9% pure; nominal concentrations of 0, 90, or 200 ppm) for 6 hours per day for 1-5 days to determine regeneration and recovery of olfactory function (Hurtt *et al.*, 1988). No clinical signs of toxicity or olfactory epithelial damage in the 90 ppm group were observed. At 200 ppm, there was a transient significant decrease (9%) in body weight at the end of the fifth exposure. The body weights of the treated group returned to control values by day 47 after exposure. Extensive destruction of the olfactory epithelium of the dorsal meatus, nasal septum and lateral walls, and the complex ethmoid turbinates was evident after a single 6-hour exposure to 200 ppm. The olfactory degeneration was characterized by epithelial disruption, fragmentation, and exfoliation. The basal cell layer remained intact. Regeneration of the epithelium with the replacement by a squamous epithelium was evident by day 3 of exposure and was essentially complete by 10 weeks after exposure. However, some minor defects were not repaired such as: adhesions between the turbinates and adjacent structures, thinning of the olfactory epithelium due to a paucity of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). Olfactory function, as determined by the ability of food-deprived rats to find buried food pellets, was affected only in rats treated at 200 ppm. The impairment of the olfactory function was temporary with recovery by 4 to 6 days after exposure but before complete regeneration of the olfactory epithelium. The NOEL was 90 ppm based on olfactory damage at 200 ppm.

In a similar experiment, rats (strain not specified) were exposed to methyl bromide (purity not specified, a nominal concentration of 200 ppm) for only 4 hours per day, 4 days per weeks for 2 weeks (Hastings, 1990). After a single 4-hour exposure, the olfactory epithelium was extensively damaged, and olfactory function was impaired. After the end of exposure, no overt signs of toxicity were observed. The epithelium began to repair immediately after exposure but required more than 30 days for the restoration to a near normal appearance. Consistent with the findings of Hurtt *et al.* (1988), olfactory function returned to normal before complete epithelial regeneration.

CD rats (15/sex/group) were exposed to methyl bromide (>99% pure; nominal concentration of 0, 30, 100, or 350 ppm) for a single 6-hour inhalation exposure (Driscoll and Hurley, 1993). Testing was done at pre-exposure, within 3 hour post-exposure, 7 days post-exposure, and 14 days post-exposure using an automated assessment of motor activity and a Functional Observation Battery. Rats were sacrificed 16 to 19 days post-exposure. There were no effects on survival, body weight, and brain weight. No histological lesions were noted in the nervous system or the nasal tissues of the 350 ppm rats. Neurobehavioral effects were only seen in the 350 ppm group tested 3 hours post-exposure. Findings included: decreased arousal (both sexes); increased incidences of drooping or half-shut eyelids (both sexes); increased urination (females only); decreased rearing (both sexes); decreased tail pinch response (males only); increased incidences of piloerection (both sexes); decreased rectal temperature (both sexes); abnormal air righting reflex (females only); and decreased motor activity (both sexes). The NOAEL was 100 ppm based on neurobehavioral effects at 350 ppm.

The biochemical effects of methyl bromide were studied by Hurtt and Working (1988), Jaskot *et al.* (1988), and Davenport *et al.* (1992). Adult male Fischer 344 rats were exposed to methyl bromide (99.9% pure; 0, or a nominal concentration of 200 ppm) by inhalation for 6 hours per day for 5 days (Hurtt and Working, 1988). Rats were sacrificed on days 1 (first day of

exposure), 3, 5, 6, 8, 10, 17, 24, 38, 52, and 73. Methyl bromide did not affect testis weight, testicular and epididymal histology, daily sperm production, cauda epididymal sperm count, sperm morphology, sperm motility, and linear sperm velocity, or cause any observable toxicity. At day 5, the methyl bromide treated group weighed approximately 10% less than the control group and continued to weigh less until day 52. The nonprotein sulfhydryl levels of the testis and liver were significantly ($p \leq 0.05$) decreased after 1 and 3 days of treatment. The depression was transient as the levels returned to control values by day 8 (3 days after treatment). There was a transient decrease in the testosterone level during the 5-day exposure, as well as the day after exposure. The testosterone level was back to the control level by day 8.

CD rats were exposed to methyl bromide (99.5% pure, 0 or a nominal concentration of 30 ppm) for 5 or 10 days (Jaskot *et al.*, 1988). After either 5 or 10 days of exposure, there were significant ($p \leq 0.05$) decreases in the enzyme activities of glutathione (GSH) reductase and GSH transferase in the liver and increases of GSH transferase and glucose-6-phosphate dehydrogenase in the lung. The decreases were no more than 17% of the respective control values. In addition, serum chemistry showed significant ($p \leq 0.05$) decreases in the levels of blood urea nitrogen (BUN), uric acid, cholesterol, and erythrocyte cholinesterase activity, as well as an increase in leucine aminopeptidase activity.

Davenport *et al.* (1992) proposed that methyl bromide-induced neurotoxicity was due to an effect on GSH and glutathione-S-transferase in the brain. Fischer-344 rats were exposed to methyl bromide (99.9% pure; 150 ppm) for 6 hours per day for 5 days. The concentration was chosen because it did not induce brain lesions or signs of toxicity. The inhibition of GSH transferase ranged from 45 to 56% of control values and the depletion of GSH ranged from 51 to 86% for the different regions (frontal cortex, caudate nucleus, hippocampus, brain stem, and cerebellum). Pretreatment and post-treatment of rats with BW 755C (3-amino-1-[m-(trifluoro-methyl)phenyl]-2-pyrazoline), an inhibitor of monohalomethane toxicity, protected against GSH transferase inhibition in all brain regions and gave partial protection against GSH depletion. Monoamines (dopamine and serotonin in the frontal cortex, caudate nucleus, and hippocampus) and amino acids were not affected by the treatment.

Another proposed mechanism for the neurotoxicity of methyl bromide was the alteration of catecholamine levels in the brain (Honma *et al.*, 1987). Male Sprague-Dawley rats (5/group) were exposed to methyl bromide (purity not specified; nominal concentrations 0, 31, 63, 100, 125, or 250 ppm) for 8 hours. Catecholamine levels (dopamine, DA; norepinephrine, NE; homovanillic acid, HVA; 3-methoxy-4-hydroxyphenylglycol, MHPG; serotonin, and 5-hydroxyindoleacetic acid, 5HIAA) were determined in the striatum, hypothalamus, frontal cortex, midbrain, and medulla oblongata after exposure (Table 2). Dopamine levels were decreased in all regions with a lowest-effect level (LEL) of 100 ppm for the striatum. Norepinephrine was decreased (87% of control, $p<0.05$) with a LEL of 31 ppm in the hypothalamus. However, the decrease (84% of control) at the next dose of 63 ppm was not statistically significant. Homovanillic acid and MHPG were increased with a LEL of 63 ppm in the striatum, hypothalamus, and midbrain (MHPG only). Serotonin and 5HIAA were not significantly affected in any brain segment. Time course studies showed that the maximal effect was detected immediately or 2 hours after exposure for most catecholamines, and the levels returned to control levels 24 hours after exposure was stopped. There were inconsistencies in this study. First, decreased dopamine was measured in the striatum of rats exposed for 8 hours to 100 or

125 ppm methyl bromide whereas exposure at these same levels for a much longer period, 24 hours, did not affect dopamine content in Honma *et al.* (1982) (**III.C. SUBCHRONIC TOXICITY**). Second, if tyrosine hydroxylase was inhibited as proposed in Honma *et al.* (1991), one would expect that the metabolites such as HVA, "downstream" from tyrosine hydroxylase would be decreased. However, the HVA level was increased in this study.

The inhibition of tyrosine hydroxylase has been proposed as the mechanism for the reduction in dopamine levels. Male Sprague-Dawley rats (3-5/group) were exposed to methyl bromide (purity not specified; nominal concentrations of 0, 16, 31, 63, 125, or 250 ppm) for 8 hours (Honma *et al.*, 1991). Brain tyrosine hydroxylase activity (TH) in different brain segments was determined by *in vitro* (all doses) and *in vivo* (≥31 ppm) methods at 0, 1, 2, and 24 hours after exposure. Both assays indicated dose-responses for decreases in DOPA (3,4-dihydroxy phenylalanine) production. The segment with the LEL in the "*in vitro*" assay was the hypothalamus; the LEL was 16 ppm, the lowest dose tested (Table 2). The segments with the LEL in the "*in vivo*" assay were the striatum and hypothalamus; the LEL was 63 ppm, with a possible incipient effect at 31 ppm. The maximal inhibition of TH in both assays was seen with the rats sacrificed immediately after the 8 hour exposure period; significant recovery took place within two hours post-exposure and was complete by 24 hours post-exposure. The authors interpreted their findings as evidence that methyl bromide directly caused changes in the enzyme structure, presumably by methylation. However, DPR had significant questions about the findings and its relationship to other studies (additional discussion in **IV.A.1.b. Brain Monoamines and Enzyme Activity**).

The possible relationship between methyl bromide and dopamine was further investigated by testing whether rats exposed to methyl bromide were more sensitive (responsive) to the dopamine agonist apomorphine, which causes hyperactivity in rats (Honma *et al.*, 1994). Increased sensitivity to a dopamine agonist was expected if methyl bromide had damaged presynaptic neurons that use dopamine as the neurotransmitter. Also, the experiment tested whether methyl bromide affected the hypoactivity induced by the norepinephrine agonist clonidine. In the first of two assays, stereotypic oral behavior caused by an intraperitoneal injection of apomorphine was determined in male Sprague-Dawley rats (5/group) 7 days before exposure to methyl bromide and on days 1, 4, 7, 14, and 28 post-exposure. There were two types of inhalation exposure: 8 hours to 0. 25, 50, 100, or 200 ppm; and 8 hours per day for 7 consecutive days to 0, 5, 10, 25, or 50 ppm. There were no consistent dose responses for the supposed methyl bromide-induced increases in stereotypic behavior. The second assay involved measuring locomotor activity (automated-counting apparatus) after an intraperitoneal injection of apomorphine or clonidine. This assay (2 rats/dose) was conducted 7 days after exposure to 0, 10 or 50 ppm methyl bromide (8 hours/day for one day or for 7 consecutive days). Testing also was done the day before exposure to methyl bromide; in these instances, neither apomorphine nor clonidine were administered before the locomotor activity was recorded. The effect of methyl bromide on locomotor activity was uncertain as the data were only for 2 rats per dose and the variability in the mean value was not indicated.

Table 2. Alteration of catecholamine levels and tyrosine hydroxylase activity in the rat brain after acute inhalation exposure to methyl bromide.[a]

Exposure (ppm)	16	31	63	100	125	250	63	125	250
Brain Region	% control (0 hour post-exposure)						% control (2 hours post-exposure)		
Striatum									
DA		92	94	76**	81*	70**			
HVA		106	144**	145**	132	137*			
NE		89	86	66*	89	78			
MHPG		107	127*	129*	139**	142**			
TH *in vitro*	98	87	72*		61**	60**	104	85*	77*
TH *in vivo*		90	62**		40**	26**	80	69*	81*
Hypothalamus									
DA		89	89	81**	82*	73**			
HVA		101	133*	137**	114	127			
NE		87*	84	79**	73**	70**			
MHPG		107	130*	126*	126	134*			
TH *in vitro*	82*	65**	65**		59**	57**	92	85	75*
TH *in vivo*		90	72*		50**	47**	104	96	79
Frontal cortex									
DA		87	92	90	91	75*			
HVA		102	121	144**	125*	125*			
NE		86	78	68**	72*	74*			
MHPG		101	127	110	115	146**			
TH *in vitro*	100	92	87*		84*	80**	105	89	80*
TH *in vivo*		103	90		62**	39**	106	101	97
Midbrain									
DA		95	88	86	87	77			
HVA		114	133	161**	148**	150**			
NE		96	80	73*	79**	73**			
MHPG		102	121*	132**	151*	140**			
TH *in vitro*	103	97	92		87	64**	106	100	97
TH *in vivo*		96	81*		68**	53**	104	102	99
Medulla									
DA		92	90	88	89	76*			
HVA		104	120	140**	149**	137*			
NE		94	91	86	83*	86			
MHPG		100	114	108	112	139**			
TH *in vitro*	97	89	91		85	72**	106	105	89
TH *in vivo*		111	92		69*	48**	104	99	104

[a/] Data from Honma *et al.* (1987) for dopamine (DA), norepinephrine (NE), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels ; and Honma *et al.* (1991) for tyrosine hydroxylase activity (TH). Measurements were made immediately, 2 hours, or 24 hours after 8 hours of exposure. Some data were not shown (see details of the studies in the text). *, ** Significance level at $p < 0.05$ (*) or $p < 0.01$ (**) based on statistics as reported.

III.B.2. Oral- Rat

Albino rats (5/sex/group) were given methyl bromide (99.5% pure) either as a liquid or in microcapsules and mixed with corn oil (Kiplinger, 1994). In the liquid methyl bromide testing, methyl bromide was given once by gavage at 50, 100, or 150 mg/kg in initial testing and at 0, 80, 120 or 160 mg/kg in retesting. Only results from the retesting are presented in this Document. For the microcapsules groups, the reported doses were 98, 146, or 195 mg/kg. Rats were fasted for 18-20 hours prior to dosing and feed was made available 3-4 hours after dosing. Rats were observed at approximately 1, 3, and 4 hours after dosing (post-dosing day 0) and once in the morning and once in the afternoon on post-dosing days 1 through 14 (day of scheduled sacrifice). As shown in Table 3, clinical signs and death were reported for all treated groups. The mortality incidences were 0 for control groups, 2/10 (corn oil) and 1/10 (microcapsules) for low dose, 6/10 (corn oil) and 7/10 (microcapsules) for the mid-dose, and 10/10 (corn oil) and 9/10 (microcapsules) for the high dose groups. The clinical signs observed before death included: hypoactivity, ataxia, prostration, labored respiration, hypothermia, and tremors. Other findings with increased incidences included wet yellow urogenital staining and mucoid feces in the treated animals. Rats died on or before post-dosing day 2 with one death on post-dosing day 4. The LD50s for the liquid methyl bromide group were 86 mg/kg and between 120 and 160 mg/kg for females and males, respectively (combined LD50 of 104 mg/kg). The LD50s for the microencapsulated group were 105 mg/kg and 159 mg/kg for females and males, respectively (combined LD50 was 133 mg/kg).

For both the liquid and microcapsules methyl bromide groups, decreased food consumption and body weight gain were reported (Table 3). These effects were related to the dose in most cases. However, the food consumption reduction was greater for the first week than the second week. The stomach was the main organ affected regardless of how methyl bromide was mixed in corn oil. Hemorrhage, edema, and squamous cell hyperplasia were due to severe irritation of the stomach lining. To determine the relative toxicity between liquid and microencapsulated methyl bromide, DPR needs clarification on the following concerns: (1) whether the microcapsules dissolved before dosing and (2) whether the procedure for the methyl bromide content analyses was appropriate. The acute LOAELs were 80 mg/kg for liquid, and 98 mg/kg for microencapsulated methyl bromide for reduced food consumption, clinical signs, stomach lesions, and mortality in treated rats. This study was considered supplemental information by DPR.

Table 3. Clinical findings in rats after acute oral exposure.[a]

Clinical Findings	Dosage (mg/kg)						
	Control	80	120	160	98	146	195
	(---------- Corn oil----------)				(----- Microcapsules----)		
MALES							
Food Consumption	**Average (grams of feed /animal/day)**						
Week 0-1	22	2	2	1	4	2	6
Week 1-2	33	15	9	1	21	11	15
Body Weight Gain	**Average (grams/animal)**						
Week 0-2	+32	-6	-6	NA	-7	-6	+1
Clinical Signs	**Incidences[b]**						
Hypoactivity	0/5	4/5	4/5	5/5	0/5	4/5	5/5
Ataxia	0/5	1/5	2/5	3/5	0/5	1/5	2/5
Prostration	0/5	1/5	0/5	0/5	0/5	0/5	0/5
Labored respiration	0/5	1/5	1/5	1/5	0/5	1/5	0/5
Hypothermia	0/5	1/5	1/5	1/5	0/5	1/5	0/5
Tremors	0/5	0/5	0/5	1/5	0/5	1/5	0/5
Death	0/5	1/5	1/5	5/5	0/5	2/5	4/5
Histology- Stomach							
Squamous cell hyperplasia	0/5	3/5	4/5	0/5	4/5	3/5	1/5
Autolysis, hemorrhage, edema[c]	0/5	1/5	1/5	5/5	0/5	2/5	4/5
FEMALES							
Food Consumption	**Average (grams of feed /animal/day)**						
Week 0-1	15	2	1	NA	3	1	NA
Week 1-2	24	7	1	NA	9	NA	NA
Body Weight Gain	**Average (grams/animal)**						
Week 0-7	+6	-13	NA	NA	-7	NA	NA
Clinical Signs	**Incidences[b]**						
Hypoactivity	0/5	2/5	5/5	5/5	0/5	5/5	4/5
Ataxia	0/5	1/5	2/5	4/5	0/5	3/5	4/5
Prostration	0/5	0/5	2/5	1/5	0/5	1/5	2/5
Labored respiration	0/5	1/5	2/5	2/5	0/5	1/5	3/5
Hypothermia	0/5	1/5	2/5	2/5	0/5	1/5	2/5
Death	0/5	1/5	5/5	5/5	1/5	5/5	5/5
Histology- Stomach							
Squamous cell hyperplasia	0/5	4/5	0/5	0/5	3/5	0/5	0/5
Autolysis, hemorrhage, edema[c]	0/5	1/5	5/5	5/5	1/5	5/5	5/5

a/ Data from Kiplinger, 1994. NA=not available, the animals died.

b/ Incidences were expressed as number of animals affected/ total animals in the group. Death was observed on day 0 (day of dosing) to post-dose day 2 (2 days after dosing) except for one death noted on post-dose day 4. Effects were those observed during the day of dosing to post-dose day 4.

c/ These animals were found dead before scheduled sacrifice.

III.B.3. Inhalation - Rabbit

Rabbits were exposed to methyl bromide (99% pure; nominal concentrations of 0.42 mg/L to 50 mg/L or 100-13,000 ppm) by inhalation (Irish *et al.*, 1940). Paralysis was observed in some rabbits exposed at 1 mg/L (260 ppm) for 20 hours. There was an indication of lung irritation at higher concentrations, though less pronounced than that observed in the rat. The concentrations and exposure times which resulted in 100% mortality are listed in Table 1.

III.B.4. Inhalation - Mouse

Swiss-Webster mice were exposed to methyl bromide (>99.5% pure) from 0.87 to 5.93 mg/L (223-1518 ppm) for 1 hour by nose only inhalation (Alexeeff and Kilgore, 1985). At all concentrations tested, the 24-hour weight gain of the treated mice was significantly ($p \leq 0.05$) decreased by 4-16% when compared to control group. Transient hyperactivity was observed in the 2.72 and 3.82 mg/L (696 and 978 ppm) groups. Abnormal gait, passivity, and lack of grooming were evident at 3.5 mg/L (896 ppm) and higher with the earliest onset at 3 hours for 4.7 to 5.93 mg/L. Additional clinical signs included: increased depth of respiration, decreased respiration rate, tremors, fasciculation, loss of righting reflex, splayed limbs, tonic seizures, and muscular rigidity. Death occurred at 3.82 mg/L and higher levels. There was also rectal hemorrhaging with diarrhea in those animals treated at 5.77 and 5.93 mg/L, occurring within 6 hours after treatment. One week after treatment, damage was observed in the kidneys ($\geq$3.50 mg/L), liver ($\geq$3.82 mg/L), brain ($\geq$3.82 mg/L), and colon ($\geq$3.82 mg/L). Glutathione levels in livers of the 4.7 and 5.93 mg/L groups were significantly ($p \leq 0.05$) lower than the control group. The NOEL was 2.72 mg/L (696 ppm) based on mortality and other effects at 3.82 mg/L.

III.B.5. Inhalation - Dog

Dogs were exposed to methyl bromide for one day, two days, and four days in range-finding studies to select doses for a one-year exposure study (Newton, 1994a). The average measured methyl bromide concentrations ranged from 55 to 394 ppm. The dogs were observed every 15 minutes for the first hour and hourly thereafter. The results for short-term exposures are summarized in Table 4.

In the one-day experiment, dogs (1/concentration, except 2 dogs used for 314 ppm) were exposed for 7 hours to methyl bromide (233, 314, 345, 350, and 394 ppm). All dogs exhibited neurotoxicity (including tremors, hunched appearance, and labored breathing) by the seventh hour, and the earliest onset was 3 hours in the 345, 350, and 394 ppm groups. The exposure of the 394 ppm dog ended at the 6th hour because of clinical signs (mucoid nasal discharge and labored breathing). One day after exposure, the 345 and 350 ppm dogs showed moderate white nasal discharge, while the 394 ppm dog was lethargic with excessive nasal discharge, salivation, and panting. At 314 ppm, one dog showed decreased activity after 4 hours of exposure. All the dogs were observed for 3 or more days and appeared normal before they were used for the two-day study. The NOAEL for the one-day exposure was < 233 ppm for neurotoxicity.

In the two-day exposure study, dogs (3/group) were exposed to 268 ppm and 283 ppm of methyl bromide (Newton, 1994a). These dogs had been used in the one-day experiment: 268 ppm group were previously exposed to either 233, 314, or 394 ppm; while the 283 ppm group were exposed to either 314, 350, or 345 ppm. At the start of this study, all dogs appeared

clinically normal. On the first day, one of the 283 ppm dogs showed excessive salivation, labored breathing, and emesis at the 6th hour of exposure. By the 7th hour, the dogs in this group showed labored breathing (3/3), excessive salivation (2/3), and emesis (2/3). By the second day, the 283 ppm group exposure was terminated because of the following observations: severe neurotoxicity (delirium, thrashing and vocalization, tremors, traumatizing behavior, depression, ataxia, irregular gait) and abnormal respiratory sounds. The 268 ppm group dogs appeared normal on the first day. One of the dogs showed labored breathing at the 3rd to 7th hour on the second day. All dogs showed decreased activity at the 7th hour of the second day. Also, increased blood urea nitrogen and serum aspartate aminotransferase were detected in both exposure groups. The NOAEL for the two-day exposure was < 268 ppm for neurotoxicity.

The four-day exposure study used dogs that had not been exposed to methyl bromide previously (Newton, 1994a). Beagle dogs (1/sex/group) were exposed to 55 ppm and 156 ppm by inhalation for four days (7 hours/day). In the156 ppm group, one dog showed lacrimation at the fifth hour of exposure. Both dogs exposed to 156 ppm showed decreased activity, lacrimation and labored breathing during the third and fourth day of exposure. Irregular gait was observed in both dogs on the fourth day post-exposure. No abnormal signs were observed during or after exposure for the 55 ppm dogs. The NOAEL for neurotoxicity observed after 3 days of exposure was 55 ppm.

In addition to the above acute toxicity studies, the following subchronic studies were evaluated for the determination of an acute NOEL. The subchronic effects from methyl bromide exposure are further discussed in **III.C.5. Inhalation - Dog**. Beagle dogs (2-4 dogs/sex/group) were exposed to methyl bromide (100% pure) by whole body inhalation at 7 hours per day, 5 days per week, for two exposure durations (Newton, 1994b). The durations of exposure were: 23 to 24 exposure days (0, 26, 53, or 103 ppm) or 30 exposure days (24 exposure days at 11 ppm, then 6 exposure days at 158 ppm). Air concentrations stated were measured concentrations. Serum bromide levels increased with the dose at $\geq$ 26 ppm. The 158 ppm group showed decreased activity on the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). They were reported in poor condition during the final (6th) exposure and showed severe neurotoxicity with lesions to the brain, adrenal, and olfactory tissues (Table 4). No effects were observed in the 103 ppm dogs after 8 days of exposure. On day 9, some of the dogs in this group showed decreased activity (3/8) and emesis (1/8). On day 10, tremor was noted in one dog. The acute NOEL was 103 ppm for decreased activity seen in the 158 ppm group after 2 exposures and severe neurotoxicity after 6 exposures, and lack of acute effects at 103 ppm.

Table 4. The neurotoxicity of methyl bromide in dogs after acute exposure.[a]

Concentration mean ± standard deviation (ppm)	Duration of exposure[a]	First signs of neuro-toxicity and Incidence[b]	Clinical signs with additional exposure
394± 20	3 hours	hunched appearance and tremors (1/1)	hunched appearance and tremors, mucoid nasal discharge, labored breathing
350± 13	3 hours	labored breathing (1/1)	labored breathing, decreased activity,hunched appearance, tremors, excessive salivation and swallowing response
345± 8	3 hours	tremors (1/1)	tremors, labored breathing, hunched appearance, excessive salivation, and gasping
314± 6	4 hours	decreased activity (1/2)	tremors, hunched appearance, and restlessness (2/2)
283 ± 13	6 hours	salivation, labored breathing, emesis (1/3)	excessive salivation (2/3), labored breathing (3/3), and emesis (2/3)
268± 19	7 hours	no effects	day 2: labored breathing (1/3) and decreased activity (3/3)
233± 21	5 hours	trembling (1/1)	panting, rapid eye blinks, and tremors
158± 7 [c]	7 hours[c]	decreased activity (8/8)	day 3: decreased activity; day 6: severe neurotoxicity; brain, and adrenal lesions, olfactory degeneration (8/8)
156± 15	5 hours	lacrimation (1/2)	day 3 and 4: lacrimation and labored breathing (2/2), prostrate (1/2), and decreased activity (2/2); day 4 post-exposure: irregular gait (2/2)
103± 9 [c]	8 days	no effects	day 9: start of decreased activity (3/8) and emesis (1/8); day 10: tremor (1/8); week 5: cerebellar lesions (1/8) at sacrifice
53± 4 [c]	13 days	no effects	day 14: decreased activity (2/8)
55	4 days	no effects	(experiment terminated after 4 days)

a/ Data from Newton (1994 a and b). Hours of exposure for onset of neurotoxicity.
b/ Incidences as number of dogs affected/ total are shown in parentheses.
c/ Data (Newton, 1994b) is under **III.C. SUBCHRONIC TOXICITY**. The first exposure was on a Friday with no effects reported. However, decreased activity was observed during the second exposure, on the following Monday.

III.B.6. Oral - Dog

Beagle dogs (1/sex/group) were given a single oral dose of methyl bromide (100% pure; 1, 3, 5, 50, or 500 mg/kg) in capsules in a corn oil solution (Naas, 1990). There was no control group. Emesis was observed in animals treated at 3 mg/kg or higher doses. The emesis was described as white foamy, containing food, with partially dissolved capsules, and/or red material. No vomiting was observed during one week post-dosing observation period. Clinical signs were observed at 50 and 500 mg/kg groups. At 50 mg/kg, both dogs showed hypoactivity, hypothermia (body cool to touch), no pain reflexes, and soft stools. Animals treated at 500 mg/kg showed prostration, rapid heart rates, hypothermia, and were dead within one day. Gross examination of the organs of these two dogs showed dark red adrenal glands (male only), dark red kidneys (both), slight hydrocephaly (female only), and marked reddened stomach mucosa (both). Necropsy was not performed on other dogs. Because of the few number of animals involved and that the effects may be due to dosing method, a NOEL was not determined. This study was considered supplemental information by DPR.

III.B.7. Inhalation - Guinea Pig

Guinea pigs were exposed to methyl bromide (purity not specified, nominal concentrations of 0.01 to 5%, with 1% =10,000 ppm) for 5 to 810 minutes (Sayers *et al.*, 1929). No tissue damage or death was observed when the guinea pigs were exposed to 0.06% for 90 minutes, or 0.03% for 270 minutes. The mortality was 100% at 5% of methyl bromide for 15 minutes, 1.3% for 68 minutes, 0.7% for 90 minutes, or 0.23% for 170 minutes. Death occurred within 21 hours after exposure at 2.2% of methyl bromide for 35 minutes, 0.23% for 90 minutes, and 0.05% for 480 minutes. Before death, lacrimation, difficulty in breathing, and weakness were observed. Necropsy showed congestion and tissue degeneration of multiple organs (including lungs, liver, heart, kidneys, and brain).

Guinea pigs (16/group) were exposed to methyl bromide (purity not specified; nominal concentration of 100 or 220 ppm for 7.5 to 8 hours per day for 1 to 3 days (Irish *et al.*,1940). Guinea pigs at 220 ppm showed respiratory difficulty before death and lung damage. No effect was observed at 100 ppm.

III.B.8. Inhalation - Human

The effects of methyl bromide in humans after acute exposure is well-documented. A summary of the clinical signs and symptoms is provided in this section. Those studies which reported actual exposure levels are described in detail in **III.H. NEUROTOXICITY**. The signs and symptoms after methyl bromide exposure are dependent on concentration and exposure duration (von Oettingen, 1946; Rathus and Landy, 1961; Greenberg, 1971; Grant, 1974; Anger *et al.*, 1986; Gehring *et al.*, 1991; Uncini *et al.*,1990; De Haro *et al.*, 1997). Acute exposures to lethal concentrations result in early symptoms of malaise, headache, visual disturbances, nausea, and vomiting. After the early symptoms, delirium, disorientation, and excitability may also occur. There is a delayed onset of symptoms that include numbness, ataxia, tremor, myoclonus, exaggerated (or absent) deep reflexes, positive Romberg's signs, paroxysmal abnormalities of the EEG, agitation, change of personality, coma, as well as clonic and tonic convulsions. Death usually occurs within 48 hours of exposure, due to pulmonary edema leading to respiratory failure or cardiovascular collapse. Postmortem examination of the brain

showed generalized swelling and lesions, including neuronal loss (Squier *et al.*, 1992).

Nonlethal exposures to methyl bromide result in neurological effects that include the early symptoms seen in lethal exposures as well as confusion, muscular weakness, tremors, convulsions, euphoria, delirium, and psychoses. Some symptoms may persist after exposure depending on the severity of toxicity. Ataxia and myoclonus continued to be experienced by a worker one year after exposure (Rathus and Landy, 1961). In severe chronic poisoning, endogenous chloride is replaced by bromide, the ionic form of bromine, from the biotransformation of methyl bromide in the body (Blumberg and Neli, 1967).

III.B.9. Dermal - Human

Six workers (1 woman and 5 men) were exposed to methyl bromide (estimated 35 g/m^3, or 9,000 ppm) dermally during the fumigation of a castle (Hezemans-Boer *et al.*, 1988; Zwaveling *et al.*, 1987). They wore tight-fitting face masks, overalls over their daily clothing, work shoes, and polyvinylchloride gloves. Shortly after exposure, the primary complaint was burning sensation under the armpits and in the groin. No neurotoxicity was observed. Redness of the skin was noted. Approximately 8 hours after exposure, all workers developed skin lesions which consisted of sharply demarcated erythema with multiple vesicles and large bullae in areas of moisture (from perspiration) such as the axillae, groin, and submammary areas. Histopathological examination showed necrosis of keratinocytes, edema of the papillary dermis, subepidermal blistering, and preferential infiltration by neutrophils. Six days after exposure, there were signs of regeneration of the epidermis, but there was still evidence of cell necrosis and presence of neutrophils. One month after exposure, the skin lesions had disappeared with no significant scarring.

In a recent case report, a worker was exposed to methyl bromide dermally due to a leakage during a field fumigation application (Lifshitz and Gavrilov, 2000). In addition to the skin lesions (burns and blisters), peripheral neuropathy (weakness of the limbs, ataxia, paresthesia of limbs, hyperactive tendon reflexes and left Babinski sign) was observed one week following exposure. These signs persisted 3 months after exposure. While the worker was equipped with respiratory gear, the authors noted that its functionality was unknown and that the neurological effects may be due to both dermal and inhalation exposures.

III.B.10. Additional Acute Studies

Acute effects were also observed in studies described (in detail) in **III.C. SUBCHRONIC TOXICITY** and **III.G. DEVELOPMENTAL TOXICITY** and are included in Table 5.

Table 5. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for acute effects of methyl bromide from selected studies.[a]

Route/ Species	Exposure Duration[b]	Study NOEL/LOEL ppm	Human Equivalent[c] NOEL/LOEL ppm	Effects	Ref.[d]
INHALATION					
Rat	6h/dx5d	90/175	47/91	tissue degeneration (brain, adrenals, nasal cavity) neurotoxicity at higher doses (250 ppm)	1
Rat	6 h	90/200	47/104	olfactory epithelium degeneration, ↓ olfactory function	2
Rat	8h	31/63	22/44	altered brain catecholamines and tyrosine hydroxylase activity	3
		<16/16	<11/11	altered tyrosine hydroxylase activity (hypothalamus)	
Rat	6 h	100/350	52/183	changes in neurobehavioral battery	4
Mouse	1 h	696/896	113/146	abnormal gait, passivity, no grooming	5
Dog	7h	<233/233[e]	<58/58	neurotoxicity	6
	7h/dx3d	55/156	14/39	↓ activity, labored breathing, prostrate	
Dog[f]	**7h/dx1d**	**103/158**	**25/39**	**↓ activity on 2nd exposure day; brain lesions after 6 exposures (had previous exposure of 11 ppm for 24 days).**	**7**
Guinea Pig	8h/dx1-3d	100/220	31/61	respiratory difficulty, death	8
INHALATION-DEVELOPMENTAL TOXICITY STUDIES[g]					
Rat	7h/d, gd1-19	20/ 70	22/75	progeny-delayed skull ossification	9*
Rabbit	**6h/d, gd7-19**	**40/ 80**	**21/42**	**progeny-fused sternebrae, gall bladder agenesis and other effects**	**10***
ORAL			**mg/kg/day**		
Rat/gavage	1 dose (corn oil)		<80 / 80	Death, hypoactivity, ataxia, prostration, labored respiration, hypothermia, squamous cell hyperplasia in the stomach	11
Rat/gavage	1 dose (microcapsule)		<98 / 98	Death, squamous cell hyperplasia	11
DERMAL					
Human	few hours	-/9000 in air	na	skin lesions (erythema, vesicles)	12

a/ Bolded studies are those selected to derive the critical NOELs for risk characterization.

b/ Duration: min=minutes, h=hours, d=days, w=weeks, and gd=gestation days.

c/ Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only (except references 9 and 10). The adult equivalent levels would be 2-fold higher since the adult respiration rate is lower (0.26 m^3/kg/day compared to the child's 0.46 m^3/kg/day). For references 9 and 10, the equivalent levels were those for adults since the effects were observed in pregnant animals.

d/ * after reference number indicates the study was acceptable according to FIFRA guidelines. References: 1. Hurtt *et al.*, 1987; 2. Hurtt *et al.*, 1988; 3. Honma *et al.*, 1987 and 1991; 4. Driscoll and Hurley, 1993; 5. Alexeeff and Kilgore, 1985; 6. Newton, 1994a; 7. Newton, 1994b; 8. Irish *et al.*, 1940; 9. Sikov *et al.*, 1981; 10. Breslin *et al.*, 1990b; 11. Kiplinger, 1994; 12. Hezemans-Boer *et al.*, 1988.

e/ The lowest dose tested.

f/ Study described in **III.C. SUBCHRONIC TOXICITY**.

g/ Studies described in **III.G. DEVELOPMENTAL TOXICITY**.

III.C. SUBCHRONIC TOXICITY

Summary: Subchronic inhalation exposure of laboratory animals to methyl bromide resulted in altered brain catecholamine levels, decreased brain tyrosine hydroxylase activity, neurotoxicity, tissue degeneration (brain, nasal cavity, heart, testes, adrenal glands, thymus, spleen, and kidneys), and death. Based on overt signs of neurotoxicity, the dog, rabbit, and monkey were more sensitive to methyl bromide than other species (rat, mouse, and guinea pig). The primary finding after oral exposure by gavage in the rat was hyperplasia of the forestomach. A decrease in body weight gain and food consumption was observed in rats given microencapsulated methyl bromide mixed in the feed. A summary of selected subchronic studies is presented in Table 7.

III.C.1. Inhalation - Rat

Rats (strain not specified, 10-12/group) were exposed to methyl bromide (99% pure, nominal concentrations of 17 to 220 ppm) by inhalation for 7.5 to 8 hours per day, 5 days per week for 6 months or until toxicity was observed (Irish *et al.*, 1940). Methyl bromide at 220 ppm was lethal; all the rats died after 3 to 4 days. At 100 ppm after 6 or more exposures, the rats were in poor general appearance and some developed convulsions. Lung lesions were observed in 66% of the rats in the 100 ppm group. Except for the one death at 66 ppm (time of death not specified), no other effect was observed at this or lower doses.

Sprague-Dawley rats were exposed to methyl bromide (99.9% pure; nominal concentration of 65 ppm for 7.5 hours per day, 4 days per week for a total of 100 hours or 55 ppm for 6 hours per day, 5 days per week for 36 weeks (Anger *et al.*, 1981). There were no effects on sciatic and ulnar nerve conduction velocities, open field activity, or coordination.

Male Sprague-Dawley rats (5-6/group) were exposed to methyl bromide (99.94% pure; nominal concentrations 0, 1, 5, or 10 ppm) for 3 weeks (daily exposure duration not specified) (Honma *et al.*, 1982). Data were presented in graphs. There was no treatment-related change in the levels of acetylcholine in the whole brain or striatum, or cyclic AMP in the striatum. A marked decrease in cyclic GMP in the cerebellum at 5 and 10 ppm was not noted as statistically significant. The other effect at 5 ppm was an increase in dopamine in the striatum (~125% of control, $p<0.05$). However at the next dose (10 ppm), the increase was only ~111% of control and was not statistically significant. Other monamines were affected at 10 ppm. There was a decrease of norepinephrine in the hypothalamus (~35% of control, $p<0.05$), and in the cortex and hippocampus (~30% of control, $p<0.05$). Serotonin was decreased in the cortex and hippocampus (~70% of control, $p<0.05$). The NOEL was 5 ppm for decreased monoamines in the brain at 10 ppm.

Sprague-Dawley rats were exposed to methyl bromide (purity not specified) for 4 hours per day, 5 days per week at nominal concentrations of 150 ppm for 11 weeks (Kato *et al.*, 1986). No clinical signs were observed. However, there was an increase in spleen weight (113% of control). Lesions in the heart were noted as small focal necrosis of heart muscle and fibrous replacement of heart muscle. In another experiment, rats were exposed to 200, 300, or 400 ppm for 6 weeks. Paralysis of the hind limb and death were observed in both the 300 and 400 ppm groups. The first death occurred after 3 weeks of exposure at 400 ppm. Voluntary movement was inhibited in all animals of the 400 ppm group by 2 weeks of exposure. Organ weights (brain, thymus, heart, liver and spleen) were significantly ($p \leq 0.05$) lower in one or both

dose groups. Histological examination of the brain of the 400 ppm group showed spongy nerve tissue and glial cell proliferation. Atrophy of the testes, sometimes accompanied by the appearance of giant cells in the seminal tubules, was observed in the 400 ppm group. Multiple and small focal necrosis or fibrosis were observed throughout the left and right ventricles and papillary muscle of the heart in all treated groups. A dose-related increase in bromide concentration was detected only in the liver.

The brain and heart were also target organs in Fischer-344 rats exposed to methyl bromide (99.8% pure, nominal concentration of 160 ppm) for 6 hours per day, 5 days per week for 6 weeks (Eustis *et al.*, 1988). Because there was more than 50% mortality, the male rats were sacrificed after 14 exposures. At the end of the 30 exposures, the survival of the female rats was 50%. There were no treatment related findings in the parameters measured in the clinical chemistry or urinalysis. The treated rats showed curling and crossing of hindlimbs, forelimb twitching, and tremors. There were significant ($p \leq 0.05$) decreases in the body weight (68% of control), and the weights of lungs, heart, spleen, right kidney, brain, liver, and right testes of the males. For the females, significant ($p \leq 0.05$) decreases in body weight (82% of control), and the weights of lungs, right kidney, brain, and liver were observed. Pathological lesions were found in the brain (necrosis and loss of neurons in the cerebral cortex, hippocampus, and thalamus), testes (degeneration and atrophy of the seminiferous tubules), nasal olfactory epithelium (necrosis and degeneration), heart (cardiomyopathy), adrenal cortex (cytoplasmic vacuolation), liver (hepatocellular necrosis), thymus (atrophy), and spleen (lymphoid depletion).

In a longer-term study, Fischer-344 rats were exposed to methyl bromide (99.8% pure, nominal concentrations of 0, 30, 60, or 120 ppm) for 6 hours per day, 5 days per week for 13 weeks (NTP, 1992; Eustis, 1992). No mortality was observed. The body weights were decreased as early as week 6 of exposure. By 13 weeks, the body weights of the 60 and 120 ppm males were 90% and 84% of control, respectively. The brain weights of the 120 ppm groups were significantly ($p \leq 0.01$) decreased to 92% (males) and 93% (females) of control values. There were occasional neurobehavioral effects (such as decreased startle response amplitude, increased startle response latency, and decreased grip strength) in the 120 ppm groups which were significantly ($p \leq 0.05$) different from control values; however, they were not related to exposure duration. Significant ($p \leq 0.05$) decreases in the mean hematocrit, hemoglobin, and erythrocyte counts were detected in the 120 ppm females only. A significant decrease in the erythrocyte count also was noted in the 60 ppm females. An increase in the incidences of olfactory epithelial dysplasia and cysts (irregularity in mucosal thickness and focal cavity spaces) was found in both sexes of the 120 ppm groups. The NOEL was 60 ppm for neurotoxicity and olfactory epithelial dysplasia at 120 ppm.

CD rats (15/sex/group) were exposed to methyl bromide (>99% pure; nominal concentrations of 0, 30, 70, or 140 ppm) by inhalation for 6 hours per day, 5 days per week for 90 days (Norris *et al.*,1993 a and b). Neurobehavioral testing was done pre-exposure and at the end of study weeks 4, 8 and 13. Testing included automated assessments of motor activity and a Functional Observation Battery (FOB). Two 140 ppm males died on test (days 12 and 27); the latter had convulsions and tremors before dying. One other 140 ppm male that survived until the end of the study also exhibited clonic convulsions and tremors. The 140 ppm groups (both sexes) weighed significantly less than the controls, starting at study week 4 while the

70 ppm female group exhibited a body weight reduction, starting about study week 9. The mean body weights were 87% of control values on week 13 for 140 ppm groups, and 92% for the 70 ppm females.

FOB testing identified effects only in the 140 ppm groups; some effects were evident as early as study week 4. Findings included: ataxia (5 females, 1 male); decreased arousal (females only); decreased rearing activity (females only); increased hind leg splay (males only); and (possibly) abnormal air righting (males only). Motor activity testing identified effects only in the 70 ppm and 140 ppm female groups. Findings included decreased total motor activity and decreased rearing activity; both were evident as incipient effects in study week 8. Female groups exposed to methyl bromide exhibited a dose response for reduced absolute brain weight. The reductions were statistically significant ($p \leq 0.01$) for all dose levels and were 96%, 95%, and 90% of control for 30 ppm, 70 ppm, and 140 ppm, respectively. For the males, the brain weight of the 140 ppm group only was reduced (94% of control, $p \leq 0.05$). Histological findings included: brain lesions at multiple sites (four 140 ppm males; neuronal loss, neuronal necrosis, malacia); peripheral nerve degeneration and/or vacuolation (140 ppm, 2/sex affected; one 30 ppm female affected); and olfactory epithelium dysplasia (140 ppm, 3/sex affected). The NOAEL was < 30 ppm based on reduced brain weight at the lowest dose tested. Neuro-behavioral testing effects were observed at $\geq$ 70 ppm. Submission of "validation" training and positive control data (Gill, 1989 a, b, c, and d) generated 5 years before the methyl bromide testing using different personnel than those in the methyl bromide testing (Driscoll *et al.*, 1994) were considered inadequate. Therefore, this study is considered unacceptable and not upgradeable by DPR.

III.C.2. Oral - Rat

In a chronic toxicity range-finding study, Sprague-Dawley rats (15/sex/group) were given microcapsules containing methyl bromide (0, 0.1, 1.0, 10, or 100 ppm) mixed in the diet daily for 4 weeks (Tompkins, 1995). The reported average dosages for both sexes were 0.009, 0.09, 0.8, or 8 mg/kg/day. The highest nominal doses ranged from 6 to 9 mg/kg/day. All rats survived to scheduled sacrifice. No significant effects were observed in the following areas: clinical observations, hematology, serum chemistry, necropsy, absolute organ weights and organ weights relative to body weight, and histology. The NOEL for these parameters was > 100 ppm (> 8 mg/kg/day). The only statistically significant finding was decreased (91 to 92% of control) food consumption in the 100 male group for each of the four test weeks. However, the body weight gains of the 100 ppm males were significantly decreased (80% of control, $p<0.05$) only for the first week. There was no effect on the food consumption in the female groups. There was a transient decrease (77% of control, $p<0.05$) in the body weight gain of the 100 ppm females at 1 to 2 weeks.

Wistar rats were given methyl bromide (>98% pure; 0, 0.4, 2, 10, or 50 mg/kg/day) by gavage 5 days per week for 13 weeks (Danse *et al.*, 1984). At 50 mg/kg/day, there were significantly ($p \leq 0.05$) reduced body weight gain (69% and 73% of control values for 6 and 12 weeks, respectively) in the male, decreased food consumption (77-82% of control values) in both sexes, and decreased red blood cell concentration (93% of control values) in the males. Histological examination showed that there was an increase in the incidence and severity of hyperplasia of the stratified squamous epithelium of the forestomach. At 10 mg/kg/day, the hyperplasia was described as slight in 9 of 10 males and 6 of 10 females. At 50 mg/kg/day, the hyperplasia was predominantly strong and occurred in 8 of 10 of males and all females. In the original report, squamous cell carcinoma of the forestomach was reported for 13 of 20 animals treated with 50 mg/kg/day. However, re-analysis of the histological slides by a National Toxicology Program Panel concluded that the lesions were non-neoplastic (Boorman, 1984). Histological changes in the lungs were focal interstitial pneumonia in the 10 and 50 mg/kg/day groups, and slight atelectasis in the 50 mg/kg/day groups. The NOEL was 2 mg/kg/day (1.4 mg/kg/day as daily dose from adjustment for 5 days per week dosing) based on forestomach epithelial hyperplasia.

The reversibility of the lesions in the stomach was studied by Boorman *et al.* (1986). Wistar rats were given methyl bromide (>99% pure, 0 or 50 mg/kg) by gavage 5 days per week for 13, 17, 21 or 25 weeks. Pseudoepitheliomatous hyperplasia of the forestomach was observed in all treatment periods; however, there was no significant increase in the incidence with prolonged exposure. Evidence of early squamous cell carcinoma was detected in one animal after 25 weeks. In another experiment, rats were treated for 13 weeks and were sacrificed immediately afterward, 4 weeks, 8 weeks, or 12 weeks after treatment. There was an apparent regression of the hyperplasia formed at 13 weeks, as no incidence of hyperplasia was observed in animals sacrificed 12 weeks after treatment. However, adhesions, fibrosis, and mild acanthosis remained in the forestomach. The dosage for lowest-observed-effect level (LOEL) was 50 mg/kg/day (35.7 mg/kg/day as an adjusted daily dose).

In a study similar to that conducted by Boorman *et al.* (1986), Wistar rats were given methyl bromide (purity not specified) by gavage at 0, 25, or 50 mg/kg/day for 4 to 17 weeks (5 days/week) and allowed a recovery period of 4 to 9 weeks before necropsy was performed (Hubbs, 1986). In the non-glandular stomach, the squamous epithelial portion showed ulceration and pseudoepithelio-matous hyperplasia characterized by hyperkeratosis, acanthosis, and epithelial peg formation. Fibrosis was found in the muscularis mucosa or tunica muscularis. In the glandular stomach, there were submucosal lymphoid aggregates and non-lymphoid mononuclear cell infiltrates in the lamina propria. At 4 to 9 weeks after treatment, there was regression of the hyperplasia in the stomach but not the muscularis fibrosis. The LOEL was 25 mg/kg/day (17.9 mg/kg/day as an adjusted daily dose).

III.C.3. Inhalation - Mouse

In a range-finding study for a 90-day study, B6C3F1 mice (10/sex/group) were exposed to methyl bromide (99.8% pure; nominal concentrations of 0, 12, 25, 50, 100, or 200 ppm) for 6 hours per day, 5 days per week, for 14 days (NTP, 1992; Drew, 1983). Mortality occurred only at the 200 ppm groups with 4 of 10 females and 1 of 10 males surviving until terminal sacrifice. Bloody urine (both sexes) and mild hyperemia in the lungs, liver, and kidneys (females) were observed in the 200 ppm groups. No urinary bladder lesion was detected to account for the

hematuria. Neurotoxicity, manifested as trembling, jumpiness, and paralysis was noted for all exposed groups but was more prominent for the groups treated at 50 ppm and higher. There are questions as to the validity of the observations at the lower doses (12 and 25 ppm) since the observer had been cautioned to look for behavioral changes (Drew, 1983).

A decrease in body weight and neurotoxicity were also observed when B6C3F1 mice were exposed to methyl bromide (99.8% pure, a nominal concentration of 160 ppm) for 6 hours per day, 5 days per week for 2 weeks in a target organ toxicity study (Eustis *et al.*, 1988). The experiment was intended for 6 weeks but was terminated after 2 weeks since more than 50% of the animals were dead after 10 and 8 exposures for the males and females, respectively. Clinical signs included red urine, lethargy, and neurological effects (curling and crossing of the hindlimbs, forelimb twitching and tremors). Treated male and female body weights at termination were only 74% and 82% of the control values ($p \leq 0.001$, both sexes), respectively. Absolute organ weights which were significantly ($p \leq 0.05$) lower in both sexes (unless noted) included: lungs, heart, spleen (males), right kidneys (males), thymus, brain, and liver. Histological examination of the tissues showed lesions in the brain (necrosis and loss of neurons in the cerebellum and cerebral cortex), kidney (nephrosis, dilatation and increased cytoplasmic basophilia), testes (degeneration), nasal cavity (degeneration and atrophy, males), heart (cardiomyopathy), adrenal gland (atrophy of the inner-zone of the adrenal cortex, females), thymus (atrophy), and spleen (lymphoid depletion and hematopoiesis).

When B6C3F1 mice were exposed to methyl bromide (99.8% pure; nominal concentrations of 0, 10, 20, 40, 80, or 120 ppm) for 6 hours per day, 5 days per week for 13 weeks, the survival rates were 83% for the 120 ppm males and 100% for the females (NTP, 1992; Eustis, 1992). In the 120 ppm group, body weight gain was 58% of control ($p \leq 0.05$, males), and brain weights were 92 to 94% of control ($p \leq 0.01$, both sexes). Clinical signs (severe curling, crossing of the hindlimbs, and twitching of the forelimbs) were observed in the 120 ppm groups, with greater severity occurring in the males than in the females. Alterations in a few of the neurobehavioral responses were observed, primarily in the 80 ppm groups; no data were reported for the 120 ppm groups. Significant ($p \leq 0.05$) changes in the hematological parameters which were dose related included: decreased mean cell hemoglobin (40 to 120 ppm males, 120 ppm females), decreased mean cell volume (40 to 120 ppm males), increased erythrocyte count (40 to 120 ppm males), and increased hemoglobin (120 ppm males). No compound-related lesions were observed by histological examination. The NOEL was 20 ppm for changes in blood parameters at 40 ppm and neurobehavioral responses at 80 ppm.

III.C.4. Inhalation - Rabbit

Rabbits (strain unspecified) were exposed to methyl bromide (99% pure, nominal concentrations of 17, 33, or 66 ppm) by inhalation for 7.5-8 hours per day, 5 days per week during a 6-month period (Irish *et al.*, 1940). No adverse effects were observed at 17 ppm. Paralysis and lung damage occurred at the next dose (33 ppm) and higher. At 66 ppm after 14 to 46 exposures, 28 of 42 rabbits showed severe paralysis, and 14 of 42 rabbits died. Rabbits appeared to recover from the paralysis if they were removed from exposure at the first sign of paralysis.

New Zealand white rabbits (2/control, 6/treated) were exposed to methyl bromide (99.9% pure; a nominal concentration of 65 ppm for 7.5 hours per day, 25 hours per week for 4 weeks

(Anger *et al.*, 1981). The data were presented in graphs. After 4 weeks of exposure, the methyl bromide group showed a decrease in body weight which continued to decline at test week 5 (1 week after continuous exposure). After 4 days of exposure, eye blink amplitude were decreased in both control and treated groups. The decline in the control returned to pre-test level in the following week. However, in the treated group, eyeblink amplitude was decreased after additional exposure. Furthermore, during the fourth week of exposure, the rabbits did not use the hind limbs or groom themselves. The recovery of normal functions was complete for sciatic nerve conduction velocity and partial for ulner nerve conduction velocity and eyeblink amplitude when the treated rabbits were tested 6-8 weeks after exposure (Russo *et al.*, 1984).

Male New Zealand white rabbits (2 control, 6 treated) were exposed to methyl bromide (99% pure, a nominal concentration of 27 ppm) at 7.5 hours per day, 25 hours per week, for 30 weeks (Russo *et al.*, 1984). There were no treatment-related changes in sciatic and ulnar nerve conduction velocities and eyeblink reflex amplitude.

III.C.5. Inhalation - Dog

Beagle dogs (2-4 dogs/sex/group) were exposed to methyl bromide (100% pure) by whole body inhalation at 7 hours per day, 5 days per week, for three exposure durations. The durations of exposure were: 23 to 24 exposure days (0, 26, 53, or 103 ppm), 30 exposure days (24 exposure days at 11 ppm, then 6 exposure days at 158 ppm), or 34 exposure days (0 or 5 ppm) (Newton, 1994b). Air concentrations stated were measured concentrations. Serum bromide levels increased with the dose at $\geq$ 26 ppm. Body weight loss (25%) and neurotoxicity were seen in the dogs exposed to 158 ppm. These dogs showed decreased activity on the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). They were reported in poor condition during the final (6th) exposure (Table 6). The next day, three 158 ppm males had to be sacrificed due to severe toxicity (opisthotonos, irregular gait, opening and closing of the jaws and convulsions). The remaining 158 ppm dogs exhibited: nystagmus, intention tremors, ataxia, irregular gait and depression. Elevated levels of protein and bilirubin were measured in the urine of the 158 ppm dogs. Histological examinations showed that each of the 158 ppm dogs had cerebellar lesions (vacuoles in the granular layer) and olfactory degeneration; the males also had adrenal cortex findings (zona fasciculata, cytoplasmic vacuoles).

A decrease in body weight gain and less severe neurotoxicity (tremors, emesis, decreased activity during exposure but not post-exposure) were seen in the 103 ppm dogs. The loss in body weight was statistically ($p \leq 0.05$) significant for all weekly measurements for males and from week 2 on for females. A decrease in activity was noted starting on exposure day 9 involving most or all of the animals. Tremors were observed in 1 of 8 dogs on day 10. Emesis was observed in 1 dog on days 9 and 10. One 103 ppm male exhibited a cerebellar lesion similar to that seen in the 158 ppm dogs. In the 53 ppm group, a decrease in activity during exposures also was noted (in 2 dogs), starting on exposure day 14. However, no abnormal findings were reported for the 53 ppm group in post-exposure examinations. The NOAEL for 23-24 exposure days was 53 ppm for neurotoxicity at 103 ppm and 158 ppm.

The female dogs which were exposed the longest to methyl bromide (5 ppm group) had reduced absolute spleen weights (55% of control compared to 75% of control for the male group) and two 5 ppm females were observed by an animal neurologist at the end of test week 6

to be less responsive than expected. The neurologist noted that one dog was “unresponsive and motionless”, and the other dog “stood quietly, appeared depressed.” He had examined the dogs in the study on two other occasions: pre-test and at the end of week 4. However, he did not examine the dogs during week 7 exposures. From exposure days 31 to 34 (end of exposure), the report noted no abnormal activities in these dogs. The LOAEL for 34 exposure days was 5 ppm for decreased spleen weight (females) and decreased responsiveness (females).

Acute and short-term NOELs were also established from these experiments (**III.B.5. Inhalation-Dog**). The acute NOEL was 103 ppm for decreased activity seen in the 158 ppm group after 2 exposures and severe neurotoxicity after 6 exposures (Table 4).

Table 6. The neurotoxicity of methyl bromide in dogs after subchronic exposure.[a]

Concentrations mean ± sd (ppm)	Onset	Clinical Signs and Incidences[c]	Clinical Signs with Additional Exposure
158± 7 [b]	day 2	decreased activity (8/8)	severe neurotoxicity, cerebellar lesions (8/8)
103± 9	day 9	decreased activity (3/8)	day 9 to 10: emesis (1/8), tremor (1/8), decreased activity (3/8); week 5: cerebellar lesions (1/8)
53± 4	day 14	decreased activity (2/8)	
26± 1	23-24 exposures	no effects observed	
5± 0.4	30 exposures	decreased responsiveness (2/8)	

a/ Data from Newton, 1994b.
b/ The dogs were exposed to 11 ppm for 24 exposure days, then 158 ppm for 6 exposure days.
c/ Incidences as number of dogs affected/total are shown in parentheses.

III.C.6. Inhalation - Guinea Pig

Guinea pigs exposed to methyl bromide (99% pure; nominal concentrations of 0, 33, 66, 100, or 220 ppm) for 7.5 to 8 hours per day and 5 days per week showed severe intoxication only at 100 ppm and higher concentrations (Irish *et al.*, 1940). At 100 ppm, 4 of 11 animals died after 64 to 91 exposures. However, pulmonary damage was insignificant. At 200 ppm, 14 of 16 animals died after only 1 to 3 days of exposure. All showed difficulty in breathing and lung damage.

III.C.7. Inhalation - Monkey

Monkeys were exposed to methyl bromide (99% pure; nominal concentrations of 0, 33, 66, 100 ppm) for 7.5 to 8 hours per day and 5 days per week (Irish *et al.*, 1940). At 100 ppm after 11 exposures, severe convulsions were observed in the one monkey tested. At the lower concentration (66 ppm), six monkeys were tested: one became paralyzed after 25 exposures and two others became paralyzed after 45 to 57 exposures. No toxicity was observed in four monkeys exposed to 33 ppm methyl bromide for 116 to 259 exposure days.

III.C.8. Additional Studies

Additional studies for the consideration of subchronic toxicity are described in the **III.D. CHRONIC TOXICITY**, **III.F. REPRODUCTIVE TOXICITY**, and **III.G. DEVELOPMENTAL TOXICITY** and are summarized in Table 7.

Table 7. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for subchronic effects of methyl bromide.[a]

Route/ Species	Exposure Duration[b]	Study NOEL/LOEL ppm	Human equivalent NOEL/LOEL ppm	Effects	Ref.[d]
INHALATION					
Rat	8h/dx5d/w ≥6 exposures	66/100	31/47	convulsions, lung lesion	1
Rat	7.5h/dx4d/w 100 h	65/-[d]	24/-	no effects on neurobehavioral tests	2
Rat	24 h/dx3w	5/10	10/21	↓ brain monoamine levels	3
Rat	4h/dx5d/wx6w	200/300	50/75	paralysis, death	4
Rat	6h/dx5d/wx3w	<160/160[e]	<60/60	death, neurotoxicity, and tissue damage	5
Rat	6h/dx5d/wx13w	60/120	22/45	startle response, ↓grip strength olfactory epithelial dysplasia	6
Rat	6h/dx5d/wx13w	<30/30 30/70	<11/11 11/26	↓ brain weight ↓ motor activity	7
Rat[f]	6h/dx5d/w 132-145 days	3/30 3/30	2/20 2/20	F_1 parental-↓ fertility progeny-↓ body weight, ↓ brain weight (F_1), ↓ cerebral cortex width (F_1)	8*
Mouse	6h/dx5d/w x 2w	<160/160[d]	<112/112	death, tissue degeneration, ↓ body and organ weights, neurotoxicity	5
Mouse	6h/dx5d/wx13w	20/40	14/28	hematology and neurobehavioral changes at higher doses	6
Mouse[g]	6h/dx5d/wx20w	33/100	23/98	brain, heart, sternum, and olfactory epithelium lesions, neurotoxicity	6

a/ Bolded studies are those selected to derive the critical NOELs for risk characterization.
b/ Duration of exposure is indicated as : h=hours, d=days, w=weeks, m=months.
c/ Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only (except reference 8). The equivalent levels would be 2-fold higher since the adult respiration rate is lower (0.26 m^3/kg/day compared to the child's 0.46 m^3/kg/day). For reference 8, the equivalent levels were those for adults since the effects were related to pregnancy.
d/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Irish *et al.*, 1940; 2. Anger *et al.*, 1981; 3. Honma *et al.*, 1982; 4. Kato *et al.*, 1986; 5. Eustis *et al.*, 1988; 6. NTP, 1992 and Eustis, 1992; 7. Norris *et al.*, 1993a and b; 8. American Biogenics, Corp., 1986.
e/ The only dose studied or the dose at which an effect was observed at the specified duration but not necessarily the LOEL.
f/ Study described in **III.F. REPRODUCTIVE TOXICITY**.
g/ Study described in **III.D. CHRONIC TOXICITY**.

Table 7. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for subchronic effects of methyl bromide (continued).[a]

Route/ Species	Exposure Duration[b]	Study NOEL/LOEL ppm	Human equivalent NOEL/LOEL ppm	Effects	Ref.[c]
INHALATION					
Rabbit	8h/dx5d/w x<6 mon	17/33	4/9	paralysis, lung lesion	1
Rabbit	8h/dx5d/w x 14-46 exp	33/66	9/17	paralysis, death	1
Rabbit	7.5h/dx4d/wx4w	<65/65[e]	<14/14	↓ nerve conduction velocity, ↓ eyeblink reflex, paralysis	2
Rabbit	7.5h/dx4d/wx30w	27/>27	7/>7	no change in nerve conduction velocity, or eyeblink reflex 3	
Rabbit[f]	**7h/d, gd1-15**	**20/ 70**	**7/24**	**convulsion, paresis, death after 1 week**	**4**
Rabbit[f]	6h/d, gd 7-17	70/140	21/41	neurotoxicity	5
Rabbit[f]	6h/d, gd 7-19	40/80	12/23	neurotoxicity on gd 19	6*
Dog	7h/dx14d	26/53	5/9	↓ activity	7
Dog	**7h/dx34d (6w)**	**<5/5[e]**	**<1/1**	**↓ responsiveness, ↓ spleen weight**	**7**
Guinea Pig	8h/dx5d/wx47 exp	33/66	7/14	death	1
Monkey	8h/dx5d/wx11 exp	66/100	14/21	convulsion	1
Monkey	8h/dx5d/wx25 exp	33/66	7/14	convulsion, paralysis	1
ORAL		NOEL/LOEL in unadjusted	mg/kg/day adjusted[g]		
Rat	gavage, 5d/wx13w	2/10	1.4/7.1	forestomach-hyperplasia	9
Rat	gavage, 5d/wx13-25w	<50/50	<35.7/35.7	forestomach-hyperplasia, tumor	10
Rat	gavage, 5d/wx4-17w	<25/25	<17.9/17.9	forestomach-hyperplasia	11

a/ Bolded studies are those selected to derive the critical NOELs for risk characterization.
b/ Duration of exposure is indicated as : h=hours, d=days, w=weeks, exp=exposures, gd=gestational day.
c/ Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only. The equivalent levels for adults would be 2-fold higher since the adult respiration rate is lower (0.26 m^3/kg/day compared to the child's 0.46 m^3/kg/day).
d/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Irish *et al.*, 1940; 2. Anger *et al.*, 1981; 3. Russo *et al.*, 1984; 4. Sikov *et al.*, 1981; 5. Breslin *et al.*, 1990a; 6. Breslin *et al.*, 1990b; 7. Newton, 1994b; 8. Danse *et al.*, 1984; 9. Boorman *et al.*, 1986; 10. Hubbs, 1986.
e/ The only dose studied or the dose at which an effect was observed at the specified duration.
f/ Studies described in **III.G. DEVELOPMENTAL TOXICITY**.
g/ The dosages were adjusted for experiments with dosing 5 days per week to 7 days per week.

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: The nasal cavity, brain, and heart were major target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage (hyperplasia, metaplasia, and necrosis) and myocardial degeneration were observed in rats and mice. Cerebellar and cerebral degenerations were detected in mice while reduced brain weight was observed in rats. When rats were exposed to methyl bromide in microcapsules mixed in the feed, the primary effect was body weight reduction. Possible treatment-related lesions were found in the spleen, liver, pancreas, and lungs. In male dogs fed methyl bromide-fumigated feed, decreased hematocrit and hemoglobin levels were observed. A summary of the chronic toxicity studies is presented in Table 14.

III.D.1. Inhalation - Rat

Wistar rats (90/sex/group) were exposed to methyl bromide (98.8% pure; nominal concentrations of 0, 3, 30, or 90 ppm) 6 hours per day, 5 days per week (Reuzel *et al.*, 1987 and 1991). The main group for each dose consisted of 50 rats of each sex and were exposed to methyl bromide for 29 months. There were 4 satellite groups (10/sex/group except noted): week 13-14 hematology and blood chemistry analyses, week 41 behavioral effects, 1 year interim sacrifice, and 2 years interim sacrifice.

In the 90 ppm group, the 2 year and 2.5 year mortality rates for both sexes (male/female) were 52%/46% and 84%/86%, respectively. These rates were considered higher than those for the control groups which were 32% for 2 years and about 72% for 2.5 years, for both sexes. The mean body weight of the 90 ppm female group was significantly ($p \leq 0.05$) lower than that of the controls throughout most of the study with the maximal reduction (12%) at the end of the study. The mean body weight of the 90 ppm male group was significantly ($p \leq 0.05$) decreased (maximum of 6%) on occasion. Absolute kidney weights were significantly ($p \leq 0.05$) decreased in the 30 ppm (89% of control) and 90 ppm (84% of control) females, and in the 90 ppm males (85% of control) when compared to control values at the 1 year sacrifice. Absolute brain weights of the 90 ppm females were reduced at the 1-year and 2-year sacrifices (Table 8). At 29 months, the absolute brain weights were significantly decreased in the 30 ppm males and females, and the 90 ppm females. Brain weight reduction also was seen in the 90 ppm male group at 29 months but was not statistically significant probably due to the small number of survivors (n=8). The NOAEL was 3 ppm for brain weight reduction.

There were increased incidences of heart thrombi and myocardial degeneration in rats that died or were killed when moribund (Table 8). These lesions may be the cause of increased mortality in the high dose groups. Statistical comparison to the control group did not identify any increased tumor incidences. Few tumors were observed: brain glioma in the 30 ppm group (1 male and 1 female), granular cell myoblastoma in the 30 ppm group (2 males), and 90 ppm group (1 male, and 2 females), spinal cord glioma in the control (1 male) and 90 ppm group (1 female). The historical control data (1974-1988) for Wistar rats showed the following incidences (male and female, respectively): 8/873 and 3/876 for brain glioma, 2/685 and 1/701 for spinal cord glioma, and 2/873 and 8/876 for granular cell myoblastoma.

At 12-24 months, the incidences of nasal cavity lesions of the 30 and 90 ppm groups were significantly ($p \leq 0.05$) different from those of the control group (Table 8). At 24-29

months, there was a dose-related increase in the incidences of nasal cavity degeneration/ hyperplasia, heart lesions (thrombus, myocardial degeneration, and cartilaginous metaplasia), esophageal hyperkeratosis, and stomach hyperkeratosis in all treatment groups. The finding of epithelial cell degeneration/basal cell hyperplasia in the olfactory epithelium of the nasal cavity was both dose- and time-related in incidence and severity (Table 8). The lesions were described as very slight at the lower doses to moderate at the higher doses. There was thinning (atrophy) of the epithelial layer and the formation of cyst-like glandular structures in the submucosa layer. The LOAEL for the basal cell hyperplasia/degeneration were >90 ppm, 30 ppm, and 3 ppm for exposures lasting 12 months, 12-24 months, and 24-29 months, respectively. The results from the reexamination of the nasal cavity histological slides (Hardisty, 1997) did not change the LOAELs because: (1) the rereading of the slides was not conducted in accordance with standard procedures for a peer review, (2) dose response for incidence and severity remained the same with effects observed at 3 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Fischer-344/DuCrj rats (50/sex/group) were exposed to methyl bromide (99.9% pure; 0, 4, 20, or 100 ppm) by inhalation 6 hours per day, 5 days per week for 104 weeks (Gotoh *et al.*, 1994). Results in this study were reported as summary data in a brief publication. There were no effects on survival. The mean body weights of the 100 ppm (both sexes) and 20 ppm (males) were stated to be lower than controls; however, no data were included in the report. The primary effect was increased incidences ($p \leq 0.05$) of necrosis (100 ppm males), inflammation ($\geq$ 4 ppm males; 100 ppm females), and respiratory metaplasia (100 ppm males; 4 ppm females) of the olfactory epithelium. These effects occurred in the males at lower doses than in the females. The LOEL for nasal cavity inflammation and respiratory metaplasia was 4 ppm. Histological examination of the tissues showed increased incidences of pituitary adenoma (100 ppm males) and adrenal gland pheochromocytoma (4 ppm females). The significance of these findings as well as non-neoplastic findings require the evaluation of individual data, historical control data, and subchronic studies. The study was considered unacceptable and upgradeable by DPR.

Table 8. The effects of methyl bromide in rats after chronic inhalation exposure.[a]

		Methyl Bromide Concentration (ppm)			
	Exposure duration	0	3	30	90
MALE					
		Mean Absolute Organ weight (g)[b]			
Brain Weight:	1 year	2.01±0.03	2.12±0.01*	2.03±0.03	1.93±0.03
	2 year	2.09±0.07	2.15±0.02	2.08±0.03	1.99±0.06
	29 months	2.15±0.02	2.11±0.03	2.03±0.04*	2.02±0.05
Nasal Cavity:			**Incidences**		
Degeneration/ hyperplasia	12-24 months	6/30++ (20%)	1/26 (4%)	11/35 (31%)	22/39** (56%)
	24-29 months	4/36++ (11%)	12/37* (32%)	16/32*** (50%)	20/28*** (71%)
Heart:	died before end of study[c]		**Incidences**		
Cartilaginous metaplasia		1/33++	2/25	5/34	12/41**
Myocardial degeneration -moderate/severe		21/33++	16/25	8/34	36/41*
Thrombus		4/33++	3/25	10/34	20/41**
FEMALE					
		Mean Absolute Organ weight (g)[b]			
Brain Weight:	1 year	1.94±0.02	1.95±0.03	1.85±0.04	1.81±0.03**
	2 year	1.97±0.02	1.91±0.01	1.88±0.03	1.84±0.05*
	29 months	2.01±0.02	1.96±0.02	1.92±0.02*	1.77±0.06**
Nasal Cavity			**Incidences**		
Degeneration/ hyperplasia	12-24 months	7/38++ (18%)	5/34 (15%)	16/39* (41%)	26/42*** (62%)
	24-29 months	5/40++ (13%)	16/42** (38%)	15/38** (39%)	25/35*** (71%)
Heart:	died before end of study[c]		**Incidences**		
Cartilaginous metaplasia		4/41	10/33	2/35	14/51*
Myocardial degeneration -moderate/severe		13/41++	5/33	5/35	38/51**
Thrombus		5/41++	8/33	1/35	20/51*

a/ Data from Reuzel *et al.* (1987, 1991). Incidence rates were the number of animals affected/number of animals examined. Rats in the 12-24 month group were those in the 1-year and 2-year sacrifice groups, and in the main group which died before two years. Rats in the 24-29 month group were those in the main group which died between days 736 and terminal sacrifice, and those at terminal sacrifice.*,**,***; +, ++ Level of statistical significance, $p \leq 0.05$ (* or +), $p \leq 0.01$ (** or ++), or $p \leq 0.005$ (***). Significance for incidences was based on a dose-weighted chi-square trend test and the Fisher's Exact Test. For brain weights, significance was based on ANOVA and Dunnett tests.

b/ The number of animals per group for the 29 months data were: 15, 25, 16, and 8 for the males; and 18, 25, 24, and 9 for the females for 0, 3, 30, and 90 ppm, respectively.

c/ Incidences of heart lesions in those animals dead before the end of the study.

III.D.2. Dietary - Rat

Sprague-Dawley rats (70/sex/group, except for 0.5 and 2.5 ppm with 50/sex/group) were given methyl bromide in microcapsules dispersed into the granular feed for presentations to the animals for two years (Mertens, 1997). Corn oil containing methyl bromide was micro-encapsulated using starch and sucrose. Two types of microcapsules were produced. One was a blend of 7 production runs; it had a methyl bromide content of 0.48% w/w. The second type was a blend of five production runs; its methyl bromide content was 3.44% w/w. The two types of microcapsules differed also in terms of corn oil, starch, and sucrose content and age of the material at start of testing. Nominal methyl bromide concentrations in the diet were as follows: 0 (basal diet), 0 (diet containing placebo microcapsules), 0.5 , 2.5, 50 or 250 ppm. The blend containing 0.48% methyl bromide was used to prepare the two low doses while the blend containing 3.44% was used to prepare the two high doses. The highest dose tested was selected on the basis of a two-week range-finding study. The daily ration of feed varied as follows: for test weeks 0-65, males and females each received 30 and 23 g, respectively; for test weeks 66 -104, males and females received 35 and 30 g, respectively. One outcome of this feeding strategy appeared to have been that a fraction of the animals in the control and 0.5 to 50 ppm groups had their feed consumption restricted during the first 65 weeks of the study. In test week 53, interim sacrifices were performed on 18-20 rats/sex for the following dose levels: 0 (basal diet), 0 (placebo microcapsules), 50 and 250 ppm. The reported dosages (male/female) were 0, 0.02/0.03, 0.11/0.15, 2.20/2.92, or 11.10/15.12 mg/kg/day for 0, 0.5, 2.5, 50, or 250 ppm, respectively.

Survival was statistically increased in the 250 ppm male group and in the 50 and 250 ppm female groups when compared to the placebo-microcapsule groups. Body weight was reduced in the 250 ppm groups; the reduction reached a maximum (about 90% of control) in the early weeks of testing in both sexes (Table 9). A further reduction in body weight relative to the controls (placebo-microcapsule groups) did not occur despite continued exposure and reduced food consumption throughout the study (Table 9). Since a reduction in feed consumption occurred in the 250 ppm groups (both sexes) starting with the first exposure week, the body weight reduction would appear to be due mainly to the reduced feed consumption.

No treatment-related effects were reported in the following areas: clinical observations, ophthalmology, hematology, serum chemistry or urinalysis. Effects on absolute organ weights (only brain, kidneys, liver, testes/ovaries were measured) and organ weights relative to body weight appeared to be due to the body weight reduction in the 250 ppm groups; this was true for animals sacrificed at test week 52 as well as for the survivors at the end of the study. An increased incidence of dark red areas was observed on the livers of the 50 ppm females surviving to test week 104 (0 ppm, basal: 5/20; 0 ppm, placebo: 3/19; 0.5 ppm: 8/22; 2.5 ppm: 4/24; 50 ppm: 14/27; and 250 ppm, 8/29). No statistical analyses were supplied for the histology data. Also, the lesion-incidence summary table did not present autolysis and lesion-grade data and may not have been corrected for tissues lost to autolysis. Possible treatment-related effects include: increased incidence of pancreatic acinar atrophy at 250 ppm (both sexes), increased incidence of adrenal cortical hypertrophy at 250 ppm (females), and increased incidence of pulmonary arterial mineralization at 50 ppm (females). Two rare tumor types, adenocarcinoma of the prostate and endometrial stromal sarcoma of the cervix, were seen at 4% incidence only at 250 ppm. By experimental design, the histological examinations of the pancreas, prostate, spleen, adrenal glands, cervix, and uterus at the 0.5 to 50 ppm dose levels were limited to those

rats that did not survive to terminal sacrifice. Autolysis was a frequent observation in the gastrointestinal organs in rats that did not survive to the end of the study (all groups, both sexes). While an increased incidence of spongiosis hepatis was seen in the 50 ppm females, the relationship of this lesion to angiectasis and the necropsy finding of dark red liver spots that also occurred at the 50 ppm dose level needs clarification.

A possible, treatment-related findings at necropsy was an increasing incidence of splenomegaly in the 2.5 ppm and 50 ppm group; however, not all spleens were sectioned (Table 10). Histological findings on the enlarged spleens included extramedullary hematopoiesis, congestion, and lymphoma. The NOEL was 0.5 ppm (0.02 mg/kg/day for males) for increased incidences of enlarged spleens at 2.5 and 50 ppm. The incidence of splenomegaly in the 250 ppm group was not statistically different from the control groups. When first reviewed, the study was considered unacceptable pending the submission of the supplemental information regarding: range-finding study; analytical methods; cause and extent of autolysis; histological examinations for the lower dose groups; and clarification of liver gross and histological findings. Additional information was submitted and this study is considered marginally acceptable to DPR. The NRC in the review of the draft RCD/1999 considered a NOAEL of 50 ppm for this study based on decreased body weight (NRC, 2000). The enlarged spleen was not considered to be treatment-related since there was no clear dose-response relationship, histological correlates in the spleen, and effects on hematology and clinical chemistry parameters. The U.S. EPA also established a NOEL of 50 ppm for this study based on reduced body weight, body weight gain, and food consumption in both genders during the first 18 months of the study (Gross, 1999).

Fischer-344 rats were fed daily for 2 years feed fumigated with methyl bromide (99.5% purity) (Mitsumori *et al.*, 1990). After fumigation, the feed was exposed to air for 21 days until the methyl bromide level was < 20 ppm and the total bromide level was approximately 500 ppm. Diets containing 80 ppm and 200 ppm total bromide were prepared from the 500 ppm feed. Another group of rats was maintained on a diet containing 500 ppm potassium bromide. In the methyl bromide groups, there were no major adverse effects reported, except for a significant ($p \leq 0.05$) decrease in body weight (3-6% from week 60 onward). Significant increases ($p \leq 0.05$) in food and water consumption and urobilinogen were observed in both 500 ppm methyl bromide and potassium bromide treated diet groups. Since the purpose of the study was to determine the effects of residual bromide, not methyl bromide itself, this study was considered supplemental information by DPR.

Table 9. Food consumption and body weight in rats during chronic exposure to methyl bromide.[a]

Duration (weeks)	Microcap 0 ppm	Methyl Bromide concentration (ppm) 0.5	2.5	50	250 ppm	
Male	**0**	**0.02**	**0.11**	**2.20**	**11.10 mg/kg/day**	
Food Consumption (mean, g/animal/day)						% Control
0 to 1	26	26	26	25	23**	88
26 to 27	27	27	27	26	24**	89
52 to 53	27	27	28	27	25**	93
78 to 79	28	27	27	27	26	93
103 to104	25	25	19	23	23	92
Body Weight (mean, g)						
1	252	256	252	250	242**	96
26	589	600	589	575	521**	88
52	683	697	684	661	595**	87
78	760	773	762	737	691*	91
104	685	725	673	667	700	102
Female	**0**	**0.03**	**0.15**	**2.92**	**15.12 mg/kg/day**	
Food Consumption (mean, g/animal/day)						
0 to 1	18	18	18	19	17**	94
26 to 27	20	20	20	19	18**	90
52 to 53	21	21	21	21	20*	95
78 to 79	24	23	23	23	21	87
103 to104	20	20	19	19	19	95
Body Weight (mean, g)						
1	171	169	170	173	166	97
26	305	303	300	305	281**	92
52	360	359	353	359	330**	92
78	462	449	443	465	418	90
104	488	455	445	489	454	93

a/ Only selected values are presented in this Table (Mertens, 1997). There were 60 to 70 animals (Microcap, 50 ppm, and 250 ppm) or 48 to 50 animals (0.5 ppm and 2.5 ppm) per group for the first 53 weeks. From week 53 to week 104, the number of male rats per group decreased from 57 to 17 (Microcap), 49 to 16 (0.5 ppm), 50 to 16 (2.5 ppm), 59 to 22 (50 ppm), and 60 to 30 (250 ppm) for the groups. For week 53 to week 104, the number of female rats decreased from 59 to 19 (Microcap), 50 to 22 (0.5 ppm), 48 to 22 (2.5 ppm), 48 to 24 (50 ppm), and 59 to 30 ppm (250 ppm) for the groups. Statistical significance was based on the Dunnett's test with *, ** for $p < 0.05$ and $p < 0.01$, respectively. % Control was based on values for Microcapsules only as the control.

Table 10. Effects of methyl bromide in spleens of rats fed microcapsules containing methyl bromide in the feed for two years.[a]

	Micro-capsules 0 ppm	Methyl Bromide Concentrations			
		0.5 ppm	2.5 ppm	50 ppm	250 ppm
		0.02	0.11	2.2	11.0 mg/kg/day
ALL EXAMINED SPLEENS					
Enlarged[b]					
Male	2/50 (4%) (p<0.05)+	7/50 (14%) (p=0.08)	10/50 (20%) (p=0.014)**	11/50 (22%) (p=0.007)**	3/50 (6%)
Female	6/50 (12%)	4/50 (8%)	4/50 (8%)	2/52 (4%)	5/50 (10%)
Congestion					
Male	1/47 (2%)	0/34 (0%)	2/35 (6%)	2/28 (7%)	1/50 (2%)
Female	2/50 (4%)	0/28 (0%)	0/24 (0%)	0/21 (0%)	0/49 (0%)
Extramedullary hematopoiesis					
Male	8/47(17%)	9/34(27%)	10/35(29%)	7/28(25%)	12/50(24%)
Female	14/50(28%)	11/28(39%)	6/24(25%)	3/21(14%)	12/49(25%)
Lymphoma/ Leukemia					
Male	0/47 (0%)	1/34 (3%)	1/35 (3%)	1/28 (4%)	0/50 (0%)
Female	0/50 (0%)	0/28 (0%)	0/24 (0%)	0/21 (0%)	0/49 (0%)
ENLARGED SPLEENS - histological findings in male rats					
Extramedullary hematopoiesis	2/2	4/7	3/10	4/11	3/3
Congestion	0/2	0/7	0/10	2/11	0/3
Lymphoma/ Leukemia	0/2	1/7	1/10	1/11	0/3
Not Sectioned	0/2	2/7	6/10	4/11	0/3

a/ Data from Mertens, 1997.

b/ Incidence= number of animals affected/total animals examined. With the 250 ppm dose excluded, statistical significance was determined by the Fisher Exact Test with ** for $p \leq 0.01$, and the Cochran-Armitage Trend test with * for $p \leq 0.05$. Histological examination of the spleens in the 0.5, 2.5, and 50 ppm groups was limited to those rats which did not survive to terminal sacrifice. The first male rat with enlarged spleen was in the 2.5 ppm group and was found dead on day 394 of the study. Spleens dimensions were provided only for those considered enlarged. The report did not provide the criteria for the determination of enlargement.

III.D.3. Inhalation - Mouse

B6C3F1 mice (86/sex/group) were exposed to methyl bromide (99.8% pure; nominal concentrations of 0, 10, 33, or 100 ppm) 6 hours per day, 5 days per week, for 2 years (NTP, 1992; Eustis, 1992). There were interim sacrifices (~ 10/sex/group) at 6 and 15 months for the control, 10, and 33 ppm groups; and at 15 months for the 100 ppm females. Another group (10 mice/sex/group) was used for neurobehavioral testing every 3 months. The exposure of the 100 ppm group was stopped after only 20 weeks because of neurotoxicity and mortality. In this group, clinical signs indicative of neurotoxicity (tremors, paralysis, unusual gait, abnormal posture) were observed in 78% of the males and 43% of the females. The surviving animals in the 100 ppm group were observed for the duration of the study (2 years). Neurological signs in the 100 ppm groups often began to appear well after their exposure had stopped.

At the interim sacrifice of 6 months, there were no significant findings in the 10 and 33 ppm groups. At the 15-month interim sacrifice, treatment-related lesions in the brain, sternum, and heart were observed. These changes were similar to those observed after 2 years. While there was no evidence of carcinogenic effects, methyl bromide caused increased incidences of cerebellar and cerebral degeneration, myocardial degeneration, cardiomyopathy, sternal dysplasia, and olfactory epithelial necrosis and metaplasia (Table 11). Cerebellar degeneration, cerebral degeneration, myocardial degeneration, and olfactory epithelium necrosis were considered fatal lesions since higher incidences occurred in animals which died before terminal sacrifice. Heart lesions, either cardiac degeneration or chronic cardiomyopathy, were observed in 80% of the males and 69% of the females exposed to 100 ppm methyl bromide; also, the incidence of chronic cardiomyopathy in the male 33 ppm group (20%) was greater than that seen in the controls (8%). Sternal dysplasia was observed at low incidences (4-6%) in the 10 ppm and 33 ppm female groups and the 33 ppm male group but higher incidences (15-20%) in the 100 ppm groups (both sexes). Because of the rarity of this lesion, the finding at 10 ppm was considered significant. Degenerative lesions in the cerebellum were observed in 44% and 18% of the male and female 100 ppm groups, respectively. Cerebellar degeneration, sternal dysplasia, chronic cardiomyopathy, and olfactory metaplasia were observed in the 100 ppm survivors which were sacrificed at study week 104 (Table 12).

Despite the neurotoxicity observed in the 100 ppm mice before week 20, neurobehavioral testing at 3 months resulted in significant ($p \leq 0.01$) findings for only 5 and 3 of the 9 endpoints studied in the 100 ppm male and female groups, respectively. However, testing of the 100 ppm female group at 6 months resulted in significant ($p \leq 0.01$) findings in 3 of the endpoints though the survivors had not been exposed to methyl bromide for about one month. Neurobehavioral testing also found a significant ($p \leq 0.05$) decrease in locomotor activity in the 10 ppm and 33 ppm groups (both sexes) when tested at 6 months as well as 12 months (females only). Based on the neurobehavioral testing changes in locomotor activity and sternal dysplasia, the LOAEL was established at 10 ppm, the lowest test dose. This study was considered acceptable to DPR according to FIFRA guidelines. The NRC in the review of this study considered a LOEL of 100 ppm for this study since the incidences for spinal dysplasia at 10 and 33 ppm were not statistically significant from the control (NRC, 2000). In addition, the incidences of decreased locomotor activity occurred at only 1 of 8 time periods for each sex and the significance of the decrease was offset by increases (nonstatistically significant) compared to control values at other times. This difference in LOEL has no impact on the risk characterization since the critical study (Reuzel *et al.*, 1987 and 1991) has a lower NOEL compared to this study (NRC, 2000).

BDF1 mice (50/sex/group) were exposed to methyl bromide (99.9% pure; 0, 4, 16, or 64 ppm) by inhalation 6 hours per day, 5 days per week for 104 weeks (Gotoh *et al.*, 1994). There were no significant differences in survival between the groups. Results in this study were reported as summary data in a brief publication. The mean body weights of the 64 ppm (both sexes) were stated to be lower than controls; however, no data were included in the report. The primary effect was increased incidences (30% compared with 0% in controls; $p \leq 0.05$) of atrophy (slight) of the granular layer of the cerebellum of the 64 ppm group. The NOEL for cerebellar lesion was 16 ppm. Histological examination of the tissues showed increased incidences of liver adenoma (4 ppm females) and lymphoma in lymph nodes (4 ppm females). However, the significance of these findings as well as non-neoplastic findings require the evaluation of individual data, historical control data, and subchronic studies. The study was considered unacceptable and upgradeable to DPR.

Table 11. The incidences of histological lesions in mice after chronic inhalation exposure to methyl bromide.[a]

	Methyl Bromide Concentration (ppm)			
	0	10	33	100[b]
Male				
Cerebellar degeneration	0/50++	0/50	0/50	31/70** (44%)
Cerebral degeneration	0/50++	0/50	0/50	11/70** (16%)
Sternal dysplasia[c]	0/50++	0/50	3/50 (6%)	14/70** (20%)
Myocardial degeneration	0/50++	0/50	0/50	32/70** (46%)
Chronic cardiomyopathy	4/50++ (8%)	7/50 (14%)	10/50 (20%)	24/70** (34%)
Olfactory epithelium, metaplasia	0/50	0/50	1/50 (25%)	2/69 (3%)
Olfactory epithelium, necrosis	0/50++	0/50	0/50	6/69* (9%)
% Survival at the end of the study[d]	82	74	80	23
Female				
Cerebellar degeneration	0/50++	0/50	0/50	11/60** (18%)
Cerebral degeneration	0/50+	0/50	0/50	2/60 (3%)
Sternal dysplasia[c]	0/50++	2/50 (4%)	2/50 (4%)	9/60** (15%)
Myocardial degeneration	1/50++ (2%)	0/50	0/50	7/59 (12%)
Chronic cardiomyopathy	2/50++ (4%)	4/50 (8%)	2/50 (4%)	34/59** (57%)
Olfactory epithelium, metaplasia	0/50++	0/50	0/50	5/60* (9%)
Olfactory epithelium, necrosis	0/50	0/50	0/50	1/60* (2%)
% Survival at the end of the study[d]	71	82	90	65

a/ Data were from NTP, 1992 and Eustis, 1992. Overall incidence was the number of animals with lesions/number of animals examined at site. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance indicated at the control value was based on a dose-weighted chi-square trend test; significance at the dosed group was based on the logistic regression test or the life table test when a lesion was considered to be fatal.

b/ Because of high mortality, exposure of the 100 ppm group was stopped at 20 weeks. The incidence rates are for all animals in this group and included incidences before and after the termination of exposure.

c/ Sternal dysplasia also was observed at the 15 month sacrifice (one male and one female from the 33 ppm group and one female in the 100 ppm group).

d/ The percentage of survival represented the survival rates adjusted for interim evaluation, neurobehavioral study animals, and accidental deaths.

Table 12. The incidences of histological lesions in survivors of chronic inhalation exposure to methyl bromide.[a]

	Methyl Bromide Concentration (ppm)			
	0	10	33	100[b]
Male Mice				
Cerebellar degeneration	0/40++	0/37	0/40	3/16** (19%)
Sternal dysplasia	0/40++	0/37	2/40 (5%)	12/16** (75%)
Chronic cardiomyopathy	4/40++ (10%)	4/37 (11%)	9/40 (23%)	9/16** (56%)
Olfactory epithelium, metaplasia	0/40++	0/37	1/40 (3%)	2/16 (13%)
Female mice				
Cerebellar degeneration	0/36++	0/41	0/45	4/40 (10%)
Sternal dysplasia	0/36++	2/41 (5%)	2/45 (4%)	7/40** (18%)
Chronic cardiomyopathy	1/36++ (3%)	4/41 (10%)	2/45 (4%)	27/39** (69%)
Olfactory epithelium, metaplasia	0/36++	0/41	0/45	5/40* (13%)

a/ Data were from NTP, 1992 and Eustis, 1992. Overall incidence was the number of animals with lesions/number of animals examined at terminal kill. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance indicated at the control value was based on a dose-weighted chi-square trend test; the pair-wise significance at the dosed group was based on the Fisher's Exact Test.

b/ Because of high mortality, exposure of the 100 ppm group was stopped at 20 weeks. Incidence rates indicated are those of the survivors at 2 years.

III.D.4. Dietary - Dog

Methyl bromide (purity not specified) fumigated feed with bromide levels of 0, 35, 75, or 150 mg/kg/day was fed to beagles (4/group) daily for 1 year (Rosenblum *et al.*, 1960). Concentrations of methyl bromide *per se* were not determined. Lethargy and lower weight gain were observed in the high dose group; these findings were absent in the sodium bromide (100 mg/kg/day) group. Salivation, diarrhea, and death occurred in both the high dose methyl bromide and sodium bromide treated diet groups. This study was considered unacceptable to DPR due to too few animals, as well as the lack of feed analysis and necropsy/pathology data.

Beagle dogs (4/sex/dose except 8 dogs/sex at high dose) were given feed fumigated with methyl bromide 5 days per week for one year (Newton, 1996). Granular feed containing 10% corn oil was fumigated with methyl bromide at concentrations of 0, 7092, 20,000 or 116,279 ppm for one hour and degassed for one hour. One hour after the feed had been presented to the dogs, the nominal residual methyl bromide levels in the feed-corn oil admixture were: 0, 0.5, 1.5 or 5.0 ppm. Reported dosages (male/female) were: 0, 0.06/0.07, 0.13/0.12, and 0.27/0.27 mg/kg/day. In addition, test feeds presumably contained fumigation-derived products (bromide, methylation adducts, methyl chloride). While the concentrations of reaction products were not measured, because of the experimental design, their concentrations in the low-dose feed versus high-dose feed may have varied by a factor of 16. Residual methyl bromide levels were selected on the basis of discussions between the Registrant and the U.S. EPA to achieve a “safety” study (i.e., the high dose was not set on the basis of toxicity data). A new analytical procedure was developed to determine residual methyl bromide; however, the adequacy of the new procedure could not be assessed pending submission of supplemental information.

There were no clear effects on survival, cage side observations, body weight or food consumption. Possible treatment-related effects included: decreased hemoglobin and (or) hematocrit levels at 3, 6 and (or) 12 months in the high-dose male group; and decreased serum calcium (94-96% of control) at 6 and 12 months in the mid- and high-dose male group (Table 13). The incidence of thyroid C-cell hyperplasia in the male control group was 1/4 versus 5/8 in high-dose male group. Mean absolute kidney weight (82-86% of control, $p<0.05$) of the mid- and high-dose female groups were reduced; however, the effects were not statistically significant relative to terminal body weight or brain weight. Due to the experimental design, the effects seen in this study may be due to residual methyl bromide and (or) its reaction products. The NOEL was 1.5 ppm (0.13 mg/kg/day for males) based on statistically significant decrease in hemoglobin and/or hematocrit at 5 ppm (0.27 mg/kg/day). When first reviewed, this study was considered unacceptable and upgrading would require the submission of the following: 1) supplemental information regarding the analytical method; 2) historical control data for thyroid C-cell hyperplasia in males; 3) histological examination of the thyroid in the low- and mid-dose male groups and the parathyroid in three high-dose females whose tissues were not examined originally; and 4) the statistical analyses of the hemoglobin, hematocrit and serum phosphate data. Subsequently, the registrant submitted data on the analytical method, histological data for the thyroid and parathyroid, and historical control data for the thyroid (CMA Methyl Bromide Industry Panel, 1998; Auletta, 1998). Based on these data, C-cell hyperplasia was no longer considered a possible adverse effect. Validation for the analytical method used in this study has been requested. This study is considered supplemental information by DPR. The U.S. EPA did not consider the reduction in hemoglobin and hematocrit levels to be biologically significant since the mean values were within 10% of control values and within the normal range (Hansen, 1998). U.S. EPA established a NOEL of $\geq$ 5 ppm for no effects in this study.

Table 13. Selected hematology and clinical chemistry parameters in dogs exposed to methyl bromide fumigated feed.[a]

Parameters	Months	Nominal concentration in the diet (ppm)			
		0	0.5	1.5	5.0
Males					
Hematocrit %	pretest[b]	(43.8-60.7)	(43.7-49.4)	(46.1-52.3)	(43.7-52.5)
	3	51.7 (50.3-54.3)	50.7 (49.7-51.1)	50.5 (46.4-55.3)	47.7* (44.6-49.5)
	6	50.8 (49.0-52.8)	51.0 (49.2-52.4)	49.1 (47.2-50.1)	46.8* (44.0-50.8)
	12	57.2 (54.5-60.0)	54.9 (54.4-55.4)	51.7 (42.7-58.6)	51.5* (45.9-55.7)
Hemoglobin g/dL	pretest	(14.5-19.5)	(14.7-16.3)	(15.0-16.8)	(14.4-17.0)
	3	17.4 (17.0-18.2)	17.1 (16.4-17.3)	17.0 (15.7-18.6)	16.2* (15.0-17.0)
	6	17.7 (17.1-18.4)	18.0 (17.0-18.5)	17.3 (16.6-17.5)	16.6* (15.5-18.0)
	12	19.1 (18.3-20.1)	18.3 (18.2-18.5)	17.5 (14.4-19.7)	17.3* (15.6-18.2)
RBC 10^6/*u*L	3	(6.40-8.49)	(6.45-7.16)	(6.74-7.26)	(6.47-7.66)
	6	7.69 (7.48-8.13)	7.41 (7.07-7.70)	7.41 (7.23-7.74)	7.24 (6.54-7.78)
	12	7.64 (7.35-7.99)	7.62 (7.16-7.95)	7.40 (7.15-7.64)	7.23 (6.73-8.07)
		8.22 (7.93-8.68)	7.81 (7.65-8.00)	7.45 (6.44-8.04)	7.59 (6.74-8.33)
Females					
Hematocrit %	3	45.9	48.4	47.9	49.6
	6	45.4	45.3	49.5	48.9
	12	48.0	49.2	53.7*	48.3
Hemoglobin g/dL	3	15.6	16.4	16.3	16.8
	6	15.9	16.0	17.4	16.9
	12	15.8	16.3	18.0*	16.2
RBC 10^6/*u*L	3	6.76	7.21	7.26	7.46
	6	6.80	6.82	7.53	7.33
	12	6.79	7.04	7.85*	7.03

a/ Data from Newton, 1996. *, ** Statistically different from control value at $p<0.05$ and $p<0.01$, respectively. There were 4 dogs/sex at all dose levels except 8 dogs/sex at the high dose.

b/ Values in parenthesis are range for all animals. Pre-test values for weeks -3, -2 and -1 before the start of the experiment were combined.

Table 14. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of methyl bromide from chronic oral and inhalation studies.[a]

Species	Duration[b]	Study NOEL/LOEL ppm	Human equivalent[c] NOEL/LOEL ppm	Effects	Ref.[d]
INHALATION					
Rat	**6h/dx5d/w x24-29m x12-24m**	**<3/3 3/30**	**<1/1 1/11**	**olfactory epithelial hyperplasia/ degeneration**	**1***
Rat	6h/dx5d/w x24m	<4/4	<1/1	nasal inflammation and respiratory metaplasia	2
Mouse	6h/dx5d/w x24m	<10/10	<7/7	neurobehavioral changes and sternal dysplasia	3*
Mouse	6h/dx5d/w x 104w	16/64	11/45	cerebellum atrophy	2
ORAL		**ppm**	**mg/kg/day**		
Rat	2 years	0.5/2.5 50/250	0.022/ 0.11 2.2 /11.1	enlarged spleens (males) decreased body weight	4[e]
Dog[f]	1 year	1.5/5.0	0.13 / 0.27	decreased hemoglobin and hematocrit (males)	5

a/ Bolded studies are those selected to derive the critical NOELs for risk characterization.
b/ Duration of exposure is indicated as: d=days, w=weeks, m=months.
c/ Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only. The equivalent levels would be 2-fold higher since the adult respiration rate is lower (0.26 m^3/kg/day compared to the child's 0.46 m^3/kg/day).
d/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Reuzel *et al.*, 1987 and 1991; 2. Gotoh *et al.*, 1994; 3. NTP, 1992; Eustis, 1992; 4. Mertens, 1997; 5. Newton, 1996.
e/ Methyl bromide was in microcapsules mixed in the feed. This study was considered marginally acceptable to DPR (see study summary for details) .
f/ The feed was fumigated with methyl bromide and then allowed to offgas.

III.E. GENOTOXICITY

Summary: Methyl bromide was genotoxic in several *in vitro* and *in vivo* assays. It was a base-pair substitution mutagen in the *Salmonella* assays. It was a direct-acting mutagen since a liver S-9 fraction was not required for mutagenicity. It caused micronuclei formation in female mice and an increased frequency of sister chromatid exchanges in CHO cells and in mouse bone marrow cells *in vivo*. It did not induce unscheduled DNA synthesis in rat hepatocytes or cause sperm abnormalities in mice. DNA alkylation was detected in both rats and mice after *in vivo* exposure by oral, intraperitoneal, or inhalation routes while DNA damage was found in the germ cells of rats after inhalation exposure. There was some evidence of genotoxicity in workers exposed to methyl bromide. Elevated levels of sister chromatid exchanges in lymphocytes and S-methylcysteine adducts in the blood were measured in soil fumigators. An increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in the lymphocytes and an increased incidence of micronuclei in oropharyngeal cells were observed in structural fumigators. The genotoxicity studies are summarized in Table 15.

III.E.1. Gene Mutation

Methyl bromide was mutagenic to *Salmonella typhimurium* strains TA100 and TA1535, but not TA98, TA1537 or TA1538 (Simmon *et al.*, 1977; Kramers *et al.*, 1985; Moriya *et al.*, 1983; NTP, 1992). It was also mutagenic to *Escherichia coli* strains Sd-4 and WP2 hcr (Djalali-Behzad *et al.*, 1981; Moriya *et al.*, 1983), and *Saccharomyces cerevisiae* (Mortelmans and Shepherd, 1980). The positive mutagenic response was independent of the presence of rat liver S9 fraction (Kramers *et al.*, 1985; Mortelmans and Shepherd, 1980; NTP, 1992) or hamster liver S9 fraction (NTP, 1992). Methyl bromide induction of sex-linked recessive lethality in *Drosophila melanogaster* was dependent on the exposure duration (Kramers *et al.*, 1985; and McGregor, 1981). Methyl bromide was also positive for the induction of forward mutations in the mouse lymphoma L5178Y assay at both the TK and HGPRT loci (Kramers *et al.*, 1985). Of all the studies summarized above, only the study by Mortelmans and Shepherd (1980) was considered acceptable to DPR. The basis for unacceptability in other studies are given in Attachment D.

III.E.2. Structural Chromosomal Aberrations

B6C3F1 mice were exposed to methyl bromide (0, 12, 25, 50, 100, and 200 ppm) for 6 hours per day, 5 days per week for 10 exposure days (NTP, 1992). Peripheral blood from female mice of the 100 and 200 ppm groups showed increased frequencies of micronuclei formation. No effect was observed in the male mice. In the second experiment, mice were exposed to methyl bromide (0, 10, 20, 40, 80, and 120 ppm) for 6 hours per day, 5 days per week for 4, 8, or 12 weeks. No increase in the frequency of micronucleated red blood cells was observed for either sex at any sampling times. This study was considered acceptable to DPR.

No induction of micronuclei formation was observed in rats (both sexes) given methyl bromide up to 123 mg/kg by a single intraperitoneal injection (Putman and Morris, 1991). This study was considered acceptable to DPR.

Methyl bromide did not cause dominant lethal mutations in male rats nor structural chromosomal aberrations in the bone marrow cells of rats (both sexes) exposed to methyl bromide by inhalation up to 70 ppm for 5 days (McGregor, 1981).

III.E.3. Other Genotoxic Effects in Experimental Animal Studies

Methyl bromide did not induce unscheduled DNA synthesis in rat hepatocytes (Kramers *et al.*, 1985) or human embryonic intestinal cells (McGregor, 1981) under *in vitro* conditions, or cause sperm abnormalities in mice after inhalation exposure (McGregor, 1981).

Methyl bromide caused a dose-related increase in the frequency of sister chromatid exchanges in Chinese hamster ovary cells *in vitro* (Rounds, 1980) and in bone marrow cells in female mice after inhalation exposure (6 hours/day and 5 days/week) to methyl bromide at 100 and 200 ppm for 10 exposures (NTP, 1992). There was a small increase noted for the male mice and this result was considered equivocal. When another group of mice was exposed to methyl bromide (up to 120 ppm) for a longer duration (12 weeks), there was no further increase in the frequency of sister chromatid exchanges in the bone marrow cells and of micronuclei in peripheral erythrocytes (NTP, 1992). Methyl bromide did not have any effect on the bone marrow cell kinetics or erythropoiesis. The author suggested that the longer duration of exposure (12 weeks compared to 10 exposure days) may have caused changes in the metabolism or sensitivity of the bone marrow cells and resulted in a reduction of response. The NTP (1992) study was considered acceptable to DPR.

In vivo exposure of mice to methyl bromide resulted in the alkylation of tissue DNA. After exposure to methyl bromide (>98% pure; 36 ppm for 4 hours) by either inhalation or intraperitoneal routes, 7-methyl-guanine in liver and spleen DNA and methylated cysteine in hemoglobin and liver protein were detected (Djalali-Behzad *et al.*, 1981).

In the study by Gansewendt *et al.* (1991), rats were exposed to methyl bromide (96% pure) by inhalation for 6 hours (263 ppm for females, and 131 ppm for males), or by gavage (8.3 *u*moles or 0.8 mg/kg for females and 0.58 mg/kg for males). From both routes of exposure, 7-methyl guanine and O^6-methyl guanine were detected in the DNA from the liver, lung, stomach, and forestomach. The DNA adducts were considered a systemic genotoxic effect since high concentrations of the adducts were found in the stomach and forestomach DNA for both routes.

Methyl bromide (>99% purity; 0, 77, 153, or 258 ppm) was administered to Fischer 344 rats (5/group) by whole body inhalation (6 hours/day for 5 days) (Bentley, 1994). Animals were sacrificed one hour or one day after the 5th exposure. Damage to testicular DNA was determined by the alkaline-elution assay. The positive control group consisted of rats given methyl methanesulfonate. Mean body weights for the 150 and 250 ppm groups were reduced during the experiment. On the day after the 5th exposure, the mean body weight of the 150 and 250 ppm groups were 97% and 78%, respectively, of the pretreatment levels. On days 5 and 6, two rats in the 250 ppm group died, and a third rat was moribund. Signs of neurotoxicity seen in the 250 ppm group included: ataxia, spasms, diarrhea, lethargy, and prostration. Colored nasal discharge was reported for all groups (including 40% incidence in the control), but was not explained. DNA from the 250 ppm group (both sacrifice times) eluted faster (breakage of DNA into smaller pieces) than DNA from the 0 ppm group but at a comparable rate to that for the positive control. While it is clear that inhalation exposure to methyl bromide at 250 ppm resulted in DNA damage in male germ cells, the results for DNA elution rates for the 150 and 75 ppm groups was not consistent. The elution of DNA from the 150 ppm group (1 hour post-treatment sacrifice) was significantly slower (DNA as more intact or cross-linking) than the rate seen with the 0 ppm group (both sacrifice times). In the 75 ppm group, DNA from the one-day post-

treatment sacrifice groups, but not DNA from the one-hour post-treatment group, eluted faster than the DNA from the control. Also, the amount of DNA from the one-day group retained on the filters at the end of the elution was significantly less than that seen with the control. A NOEL cannot be determined at this time pending submission of the following information: protocol and raw data; historical control data; explanation of the time frame per group for inhalation exposures, sacrifices, and alkaline elution runs; and data analysis. This study is considered unacceptable by DPR according to FIFRA guidelines. The U.S. EPA concurred with the study author that the result for the 75 ppm group (one-day) did not represent a treatment-related effect (Hansen, 1994). The result at 250 ppm was considered positive for genotoxic potential to the DNA of testicular cells after inhalation exposure.

DNA methylation was studied in rats and mice after single or multiple dose exposures (Pletsa *et al.*, 1999). Sprague-Dawley rats (female, 2-4/group) were exposed to methyl bromide by gavage for 4 hours (80 or 160 mg/kg) or for 4 days (30 or 60 mg/kg). O^6-methylguanine adducts were detected in several tissues (liver, glandular stomach, and forestomach) by either treatments, and in spleens, lung, bone marrow, and blood leukocytes from multiple dosing. The multiple dosing regiment also resulted in a decrease of O^6-alkylguanine-DNA alkyltransferase, a repair enzyme, in the tissues examined. This decrease was hypothesized to be the result of inactivation by methyl bromide or reduced de novo synthesis. O^6-methylguanine adducts were also found in tissues of lamda lacZ transgenic mice after single (5 or 12.5 mg/kg) or multiple doses (25 mg/kg for 10 days). There was no increase in mutant frequency with either regiments. The hypothesis was that the adduct levels were at pre-mutagenic level and that other events, such as cell proliferation, also need to be activated for mutagenesis to occur.

III.E.4. *In vitro* and *In vivo* Human Studies

Hallier *et al.* (1993) showed a polymorphism in human blood for glutathione-S-transferase activity and methyl bromide. Of the individuals studied, 75% of them were considered conjugators; that is, there was an apparent enzyme-mediated disappearance of methyl bromide when their erythrocyte cytoplasm was incubated with methyl bromide (99% pure; 5,000 ppm) and glutathione. Individuals whose blood did not show such a reaction were considered non-conjugators. The conjugation reaction was apparently a detoxification mechanism because sister chromatid exchanges in the peripheral lymphocytes of non-conjugators were increased by approximately twofold over untreated control levels. Under identical testing conditions, lymphocytes from conjugators showed little or no increase in sister chromatid exchanges.

In a report on biomonitoring, S-methylcysteine adducts in the blood and sister chromatid exchanges in lymphocytes were measured in methyl bromide soil fumigators (Goergens *et al.*, 1994). Methyl bromide exposure levels and duration of exposure were not provided. The adduct levels in the blood ranged from 23 to 42 nmoles/g protein for 8 soil fumigators and 13-18 nmoles/g protein for 4 controls with no methyl bromide exposure. For 14 soil fumigators, there was an increase of sister chromatid exchange rates in the lymphocytes collected in September (the end of use season) compared to those collected in June (beginning of the season).

In another biomonitoring study, hemoglobin S-methycysteine levels in 14 methyl bromide workers showed a range of 5 to 35 nmoles/g protein compared to 5-10 nmoles/g protein (estimated from graph in the report) (Iwasaki *et al.*, 1989). The methyl bromide concentration in the work place was less than 2 ppm, the detection limit of the gas detector tube.

In a study on the genotoxicity of methyl bromide in humans, blood and oropharyngeal cells were collected from 32 workers involved in structural fumigation (Calvert *et al*., 1998a). Oropharyngeal cells were used to indicate recent exposure since the average lifespan for these cells is 14 days. Compared to individuals with no history of methyl bromide exposure (28 referents), samples from workers showed an increased incidence of micronuclei in oropharyngeal cells, and an increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in lymphocytes. No consistent differences were observed for the frequencies of kinetochore-negative lymphocyte micronuclei, or kinetochore-positive lymphocyte micronuclei. The limitations of the study included: small sample size, inadequate exposure information, and short duration of exposure (median length was 4 hours). The authors did conclude that the findings provided some evidence of genotoxicity in humans after short-term exposure to methyl bromide.

Table 15. The genotoxicity of methyl bromide.

Test types	Route/ Exposure Duration[a]	Dose[b]	Effects/Comments	References[c]
I. Gene Mutation				
Bacterial mutagenicity tests				
S. typhimurium, TA100	air, x 21 h	≥ 0.01%	+, dose-related increase in revertants	1
S. typhimurium, TA100	air, x 5 d	≥ 1900 mg/m^3	+, ± rat liver S9 fraction	2
S. typhimurium, TA100	air	≥ 500 mg/m^3	+	3
S. typhimurium, TA100	air	≥ 0.004 moles/L	+, ± rat or hamster liver S9 fraction	4
S. typhimurium, TA98	air	> 50,000 mg/m^3	–	2
S. typhimurium, TA98	air	> 2.4 moles/L	–	4
S. typhimurium, TA1535	air, x 2 d	≥ 5000 *u*g/plate	+	3
S. typhimurium, TA1537, TA1538,TA98	air	> 5000 *u*g/plate	–	3
E. coli Sd-4	solution	≥ 4 mM	+	5
E. coli WP2 hcr	air, x 2 d	5000 *u*g/plate	+	3
Mitotic recombination				
S. cerevisiae	solution, x 4 d	≥ 0.2%	+, ± rat liver S9 fraction	6*
Sex-linked recessive lethal test				
D. melanogaster	air, x 5 h	> 70 ppm	–	7
D. melanogaster	air, x 6 h/d x 5 or 15 d	≥ 200 mg/m^3	+	2
Forward mutation test (Mouse lymphoma L5178Y)				
TK locus and HGPRT locus	solution, x 24 h	0.3 mg/L	+	2
II. Structural Chromosomal Aberrations				
Micronucleus test				
Mouse	intraperitoneal	> 123 mg/kg	–, in bone marrow cells	8*
Mouse	inhalation, 6h/dx5d/wx2w	≥ 100 ppm	+, in peripheral red blood cells (females)	4*
Mouse	inhalation, 6h/dx5d/wx12w	> 120 ppm	–, in peripheral red blood cells	4*

a/ The duration of exposure was: h= hrs, d=days, and w=weeks.

b/ Dose was the concentration of methyl bromide which resulted in a positive response or the highest dose tested with a negative response.

c/ * indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Simmon *et al.*, 1977; 2. Kramers *et al.*, 1985; 3. Moriya *et al.*, 1983; 4. NTP, 1992; 5. Djalali-Behzad *et al.*, 1981; 6. Mortelmans and Shepherd, 1980; 7. McGregor, 1981; 8. Putman and Morris,1991.

Table 15. The genotoxicity of methyl bromide (continued).

Test types	Route/ Exposure Duration[a]	Dose[b]	Effects/Comments	References[c]
Chromosomal aberration test				
Rat	inhalation, 7 h/dx5d	> 70 ppm	–, in bone marrow cells	1
Dominant lethal test				
Rat	inhalation, 7 h/dx5d	> 70 ppm	–, no genotoxicity or reproductive effects	1
III. Other Genotoxic Effects				
Unscheduled DNA synthesis				
Rat hepatocytes	solution, x 24 h	> 0.3 mM	–, no increase in nuclear grain counts	2
Human embryonic intestinal cell	air, x 3 h	> 70%	–, no increase in nuclear grain counts	1
Sister chromatid exchange				
CHO cells	air, x 18 h	≥ 1 ppm	+, dose related ↑ in frequency	3
Mouse	inhalation, 6h/dx5d/wx2w	≥ 100 ppm	+, dose related ↑ in frequency (females)	4*
Mouse	inhalation, 6h/dx5d/wx12w	> 120 ppm	–	4*
Human lymphocytes	air, x 1hr	5,000 ppm	+, non-conjugators	5
Alkylation				
Mouse	inhalation x 4 h	36 ppm[d]	+, N-7-methylguanine in liver and spleen DNA and methylated cysteine in hemoglobin and liver protein	6
Mouse	intraperitoneal	417 *u*g/kg	+, alkylation protein in hemoglobin and liver	6
Rat	inhalation x 6 h or single dose by gavage	131-263 ppm 0.58-0.8 mg/kg	+, methylated guanine in liver, lung, stomach and forestomach	7
Sperm abnormality				
Mouse	inhalation, 7h/dx5d	> 70 ppm	–, no increase in frequency of abnormally shaped sperm	1
Micronuclei and hprt mutation				
Humans	inhalation, not reported	not reported	+ (weak), micronuclei and hprt mutations	8

a/ The duration of exposure was: h= hrs, d=days, and w=weeks.

b/ Dose was the concentration of methyl bromide which resulted in a positive response or the highest dose tested with a negative response.

c/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. McGregor, 1981; 2. Kramers *et al.*, 1985; 3. Rounds, 1980; 4. NTP, 1992; 5. Hallier *et al.*, 1993; 6. Djalali-Behzad *et al.*, 1981; 7. Gansewendt *et al.*, 1991; 8. Calvert *et al.*, 1998a.

d/ Static exposure.

III.F. REPRODUCTIVE TOXICITY

Summary: In a 2-generation reproductive toxicity study in rats by inhalation, methyl bromide reduced the fertility rate of the F_1 parents during the second mating trial. While the body weights of the treated pups at birth showed varied responses, their body weights were significantly lowered during lactation. Brain weight and cerebral cortex width were reduced in the F_1 adults.

III.F.1. Inhalation - Rat

Methyl bromide (99.9% pure) was administered to Sprague Dawley rats of both sexes by whole-body inhalation 6 hours per day and 5 days per week at the nominal concentrations of 0, 3, 30, or 90 ppm (American Biogenics Corp., 1986; Hardisty, 1992; Busey, 1993). Parental animals were exposed for about 40 or 55 days and 90 to 105 days before their first and second matings, respectively, and were exposed for a total of 132-145 days before they were sacrificed. There was no exposure to methyl bromide between gestation day 21 and lactation day 4 in any of the four birthing periods. The pups were not directly exposed to methyl bromide until after weaning (post-natal day 28). Body weights (91-95% of control values) and body weight gain (76% of control values) during the pre-mating periods were significantly decreased only in the F_0 males of the 90 ppm group. For the 30 and 90 ppm F_1 groups, the body weights at pre-mating and during reproduction were consistently lower than those of controls. The absolute brain (wet) weights of the F_0 males, F_1 males, and F_1 females in the 90 ppm groups were significantly ($p \leq 0.05$) decreased by 5%, 6%, and 6%, respectively, compared with controls (Table 16). The brain weight of the F_1 females of the 30 ppm group was also reduced by 5% ($p > 0.05$). Fertility indices (the ratio of the number of pregnancies to the number of copulations) were comparable among the four treatment groups (85-100% of control) for the F_{1a}, F_{1b}, and F_{2a} mating trials. However, in the F_{2b} mating trial, the fertility indices decreased from 90.9 of the controls to 66.7% (p=0.056, Fisher's Exact test) and 68.2% (p=0.066, Fisher's Exact test) in the 30 and 90 ppm groups.

At birth, the pup body weights of the treated groups were either higher or not significantly different from controls; the only exception was the lowered body weight of the F_{2a} 90 ppm group (Table 16). During lactation, the F_{1a} and F_{1b} pups of the 30 and 90 ppm groups showed significantly reduced body weights on lactation days 14 to 28. The F_{2a} 90 ppm pup body weights were lower at birth than the controls and remained reduced throughout lactation. The F_{2a} 30 ppm pup body weights showed significant reduction on lactation days 14 to 28. The F_{2b} 30 and 90 ppm pup body weights were decreased, starting as early as 4 days after birth. The reduction in body weight was greater in the F_{2a} and F_{2b} progeny (reduction of 9 to 21% at 90 ppm) compared respectively to the F_{1a} and F_{1b} pups (reduction of 5 to 11% at 90 ppm). Since the pups were not exposed to methyl bromide during the lactation period, except perhaps via the maternal milk, the finding of reduced body weights suggested that growth retardation might be an effect due to the 14 to 15 days of *in utero* exposure.

For the female F_{2b} progeny from the 90 ppm group, the absolute weights of the brain, heart, kidneys, and liver were reduced significantly ($p \leq 0.05$) by 7%, 15%, 18%, and 23% when compared to control values, respectively. The absolute weights of the kidneys, liver, and testes of the corresponding male progeny were also reduced, though to a lesser degree. The organ to body weight ratios were generally not significantly different from control values.

Histomorphometric data showed a decrease in the width of the cerebral cortex (parameters IIIh and IVb in the sectioning scheme of Rodier and Gramann, 1979) of the F_1 90 ppm groups (both sexes) (Table 16). Measurements for other parameters also were decreased in the F_1 90 ppm females (IIh, IVb) or F_1 males (IIIa and IIId). Since the mid- and low-dose F_1 groups were not examined, no NOAEL was established for these effects. However, the reduced brain (fixed) weights for the F_1 30 ppm females suggested that the LOAEL for the reduced cerebral-cortex width was 30 ppm. Histomorphometric parameters were not affected in the F_0 90 ppm adults which suggested that the F_1 effects were the result of the *in utero* exposure of the F_1 animals or via feeding in the milk. However, there are no published studies on the excretion of methyl bromide in the milk. Disse *et al.* (1996) showed the presence of bromide in the milk of rats exposed to sodium bromide (250 mg/%) in the drinking water, *ad libitum*, from gestation day 5 to 15.

The parental NOAEL was 3 ppm based on reduced fertility. The progeny NOEL was 3 ppm based on the decreased pup body weights and organ weights, reduced F_1 adult brain weight, and reduced cerebral cortex width assumed at 30 ppm. This study was considered marginally acceptable to DPR according to FIFRA guidelines. In the evaluation of this study, U.S. EPA established the NOEL for maternal toxicity at 30 ppm based on reduced body weights. Reduced fertility was considered a treatment-related finding and an indicator of reproductive toxicity (U.S. EPA, 1992a).

III.F.2. Oral - Rat

In a published study to investigate the effects of methyl-bromide fumigated feeds, Crj:CD (SD) rats (24/sex/group) were given either basal diet or fumigated feed (80 ppm, 200 ppm, or 500 ppm total bromine) for 18 weeks for each generation (Kaneda *et al.*, 1993). The methyl bromide concentration was reported as < 20 ppb but no details were given. Using the average consumption rates provided in the report, the exposure in terms of methyl bromide was approximately 200 ng/kg/day using average body weights of 0.35 kg and 0.25 kg for males and females, respectively, and consumption rates of 25 g/week and 20 g/week for males and females, respectively. The only significant effects were reduced food consumption in the 500 ppm total bromide F1 parental females during the weeks 9 and 10 of the premating period and on days 0 to 21 of lactation (87-93% of controls), and lowered body weights throughout the lactation period of 500 ppm total bromide F2 female pups (91-95% of controls). A NOEL for reproductive effects for methyl bromide can not be established since methyl bromide levels in the feed were not determined.

Table 16. Body weight changes in rats after inhalation exposure to methyl bromide in a 2-generation reproductive toxicity study.[a]

Mean Body Weights (grams)[b]

Lactation	F_{1a} litter				F_{1b} litter			
Days	0	3	30	90 ppm	0	3	30	90 ppm
0	6.0	6.2**	6.2**	6.0	6.2	6.4**	6.2	6.5**
4	9.5	9.4	9.3	9.3	9.3	9.9**	9.5	9.7*
7	13.5	13.7	13.0*	13.1	13.7	14.9**	14.1	14.3
14	23.2	22.9	21.5**	21.6**	24.1	24.2	22.5*	22.5*
21	37.8	37.7	34.3**	33.8**	39.3	39.4	36.0**	36.4**
28	68.4	66.9	62.1**	61.8**	70.1	69.3	64.1**	66.4

Lactation	F_{2a} litter				F_{2b} litter			
Days	0	3	30	90 ppm	0	3	30	90 ppm
0	5.6	6.1**	5.5	5.4**	6.4	6.7**	6.2	6.2
4	8.1	8.4	7.8	7.4**	10.1	9.9	9.2**	9.2**
7	11.6	12.2*	11.6	10.6**	14.3	14.7	13.4*	13.3*
14	21.9	22.6	20.4**	18.6**	24.1	23.7	19.8**	19.6**
21	35.4	36.2	31.4**	29.1**	40.3	39.8	32.4**	32.0**
28	64.3	64.2	58.6**	53.8**	71.6	70.6	58.4**	58.2**

Mean Absolute Brain (wet) Weight (grams)[c]

ppm	F0 Adults		F1 Adults		F2 Weanlings	
	males	females	males	females	males	females
0	2.26	2.11	2.16	2.05	1.57	1.53
3	2.25	2.09	2.15	2.04	1.54	1.48
30	2.20	2.11	2.14	1.95	1.51	1.45
90	2.14*	2.07	2.02*	1.93*	1.49	1.42 **

Mean Cerebral Cortex Width (mm, mean ± standard deviation)[d] for F1 Adults

ppm	Males		Females	
	IIIh	IVb	IIIh	IVb
0	1.41±0.130	1.47±0.149	1.38±0.163	1.43±0.092
90	1.30±0.143*	1.42±0.121	1.28±0.115*	1.37±0.086*

a/ Data from American Biogenics Corp., 1986. Fetuses were exposed *in utero* to methyl bromide for 5 days/week during gestation days 0 to 19. Offspring were not placed in the inhalation chambers during the lactation period.

b/ Values were mean body weights for both sexes. Statistical significance levels were * at $p \leq 0.05$, and ** at $p \leq 0.01$ levels using ANOVA and Scheffe's Multiple comparisons reported by the investigators.

c/ Statistical significance levels were * at $p \leq 0.05$, and **at $p \leq 0.01$ levels.

d/ Data from Busey, 1993. IIIh and IVb are sections of the brain based on Rodier and Gramann (1979).

III.G. DEVELOPMENTAL TOXICITY

Summary: Methyl bromide caused developmental effects in both rats and rabbits after inhalation exposure. The findings in the fetuses included delayed skull ossification in rats and fused sternebrae, gall bladder agenesis, and other effects in rabbits. Methyl bromide did not cause any significant developmental effects in rats and rabbits after oral exposure.

III.G.1. Inhalation - Rat

Pregnant Wistar rats were exposed to methyl bromide (99.5% pure; nominal concentrations of 0, 20, or 70 ppm) for 7 hours per day from days 1 to 19 of gestation (Sikov *et al.*, 1981). Additional groups received a pre-gestational exposure to methyl bromide (20 and 70 ppm) for 5 days per week for the three weeks before mating. There was no significant maternal toxicity, with and without pre-mating exposure, and the NOEL was greater than 70 ppm. The only developmental effect was an increased incidence of delayed skull ossification in the fetuses of both 70 ppm groups, with the developmental NOEL at 20 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

III.G.2. Inhalation - Rabbit

Pregnant New Zealand white rabbits (26/group) were exposed to methyl bromide (99.5% pure; nominal concentrations of 0, 20, or 70 ppm) 7 hours per day from days 1 to 24 of gestation (Sikov *et al.*, 1981). Maternal toxicity was observed only in the 70 ppm group. After 3 days of exposure and throughout the study, food consumption of the 70 ppm group was lower than the other groups. After approximately 1 week of exposure, the 70 ppm does showed a decrease in body weight and signs of neurotoxicity (convulsive movements, severe to partial paresis of the hind limb). The first doe died on gestation day 9, and two more does died on gestation day 10. Even though dosing stopped on gestation day 15 for all treatment groups (Hardin *et al.,*1981), all but one of the 70 ppm does were dead by gestation day 30. The NOEL for maternal neurotoxicity was 20 ppm. No developmental toxicity was observed in the fetuses of the 20 ppm group or those (8 fetuses/1 litter) of the one survivor from the 70 ppm group. Because of the loss of the 70 ppm group and the abbreviated duration of gestational exposure in the 20 ppm group, this study was not a valid developmental toxicity study according to FIFRA guidelines.

In a probe study to determine the maternal toxicity and embryo lethality of methyl bromide, pregnant New Zealand white rabbits (7/group) were exposed to methyl bromide (99.6% pure; nominal concentrations of 0, 10, 30, or 50 ppm in Part I; and 0, 50, 70, or 140 ppm in Part II) 6 hours per day by inhalation on days 7 to 19 of gestation (Breslin *et al.*, 1990a). All animals were sacrificed on gestation day 20 except for the 140 ppm group which was sacrificed on gestation day 17 due to their moribund state. No toxicity was observed in Part I.

In Part II, the does in the 140 ppm group showed early signs of toxicity (lethargy and decreased food consumption) after 8 exposures. With continued exposure, the treatment related effects were: decreased body weights and body weight gains; and neurotoxicity (lethargy, labored breathing, ataxia, right-sided head tilt, reduced sensations in the extremities, dilated pupils, lateral recumbency, loss of placing or righting reflex, and rear leg splay). Histological examination of the brains from the 140 ppm group showed pathological lesions in

all animals (multi-focal areas of inflammation of the meninges overlying most regions of the brain and/or bilaterally symmetrical necrosis or spongiosis of the midbrain dorsolateral to the pyramidal tracts). Fetal examinations were limited to counting the number of implantations and resorptions. In the 70 ppm group, there appeared to be a reduction in litter size in association with an increase in pre-implantation loss. However, the loss was not considered treatment-related since implantation occurred before treatment. No examination of the 140 ppm group was reported. This study was considered supplemental information to DPR.

In the definitive study by the same group of investigators, pregnant New Zealand white rabbits were exposed to methyl bromide (99.6% pure; nominal concentrations of 0, 20, 40, or 80 ppm in Part I; and 0 or 80 ppm in Part II) for 6 hours per day by inhalation from days 7 to 19 of gestation (Breslin *et al.*, 1990b). The Part II experiment was designed to determine if the gall bladder agenesis observed in Part I was associated with a particular male used for artificial insemination. Rabbits (in Part II) designated as naive controls were inseminated with sperm from the suspect male.

Maternal effects were observed only in the 80 ppm group and included: decreased body weight gain (Parts I and II), decreased feces, and neurotoxicity (3 of 26 rabbits in Part I only; lethargy, right-sided head tilt, slight ataxia, and slight lateral recumbency). Neurotoxicity was observed on gestation day 19, the last day of exposure. The body weight gain was reduced in both Part I and II 80 ppm groups, but only the reduction in Part II was statistically significant ($p \leq 0.05$). This reduction in maternal body weight gain in the 80 ppm group in Part II was seen in the presence of reduced fetal weight. DPR estimated the maternal body weight as the difference between terminal body weight and gravid uterine weight and showed that there was no difference between the control and treated groups (Table 17). In addition, the significance of any maternal body weight gain reduction is uncertain because body weight changes in rabbits during pregnancy are more variable than other species (U.S. EPA, 1991). The maternal NOEL was 40 ppm based on neurotoxicity.

Fetal effects were also observed primarily in the 80 ppm groups (Table 17). The fetal effects included omphalocele, hemorrhaging (with or without generalized edema), retro-esophageal right subclavian artery, gall bladder agenesis, fused sternebrae, and decreased fetal body weight (13% in Part II). In the 80 ppm group (Part I), the incidences of gall bladder agenesis and fused sternebrae were significantly ($p \leq 0.05$) different from the controls. The increased incidences of gall bladder agenesis and fused sternebrae were independent of maternal toxicity because these effects were observed in fetuses from both normally behaving and affected (with neurotoxicity) does. The finding of gall bladder agenesis was confirmed in Part II with approximately the same litter incidence (29%) as for Part I (26%). Additionally, gall bladder agenesis was not associated with a particular male since the malformation was not observed in the naive controls (in Part II) which had been inseminated only with sperm from the suspect male. The historical control incidences of gall bladder agenesis are in Attachment B. The distribution of affected fetuses with respect to neurotoxicity in the does is shown in the footnotes of Table 17. The developmental NOEL was 40 ppm based on omphalocele, hemorrhaging, retro-esophageal right subclavian artery, gallbladder agenesis, fused sternebrae and decreased fetal body weight at 80 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 17. The incidences of fetal effects in rabbits after inhalation exposure to methyl bromide during gestation.[a]

	Methyl bromide Concentrations						
	Part I				Part II		
Effects[b]	0	20	40	80ppm	0	0[c]	80ppm
# Examined:							
fetuses	190	137	143	159	114	102	92
litters	21	15	19	19	16	13	14
Fetal body weight (g)	31.8	32.2	35.0	30.4	36.2	33.8	31.4*
External Effects							
omphalocele	0	0	0	2/2 (11%)[d]	0	0	0
hemorrhage (with or without edema)	0	0	0	2/2 (11%)[d]	0	0	1/1 (7%)[d]
Soft Tissues							
retro-esophageal right subclavian artery	0	0	0	2/2 (11%)[d]	0	0	0
gall bladder agenesis	2/1 (5%)	1/1 (7%)	1/1 (5%)	13/5*[e] (26%)[d]	1/1 (6%)	0	4/4[e] (29%)[d]
Skeletal Effects							
fused sternebrae	0	0	3/2 (11%)	20/10*[f] (53%)[d]	NA[g]	NA[g]	NA[g]
Maternal							
Terminal body weight-gravid uterine weight (grams,day 28)	3863	3659	3805	3636	3428	3391	3344

a/ Incidence data were expressed as the number of fetuses affected/number of litters affected. Data were from Breslin *et al.* (1990b) with does exposed to methyl bromide 6 hours/day on days 7 to 19 of gestation. Parts I and II were two separate experiments. Statistical significance in comparison to the controls, * ($p \leq 0.05$), is indicated after each incidence.

b/ Omphalocele is the protrusion of intestines through a defect in the abdominal wall at the umbilicus. Hemorrhage is subdermal hematoma with either multiple petechiae or edema. Retro-esophageal right subclavian artery refers to the placement of the artery posterior to the esophagus. Fused sternebrae is the premature fusion of the sternum segments.

c/ These rabbits were designated as naive controls and were inseminated with sperm from suspect male.

d/ Percent of litters affected= (affected litters/total litters examined) x 100.

e/ Of the 13 fetuses with missing gall bladder in Part I, 6 were from 3 does without neurotoxicity and 7 were from 2 does with neurotoxicity. In part II, all 4 affected fetuses were from 4 does without neurotoxicity.

f/ Of the 20 fetuses with fused sternebrae, 19 were from 9 does without neurotoxicity, and 1 from 1 doe with neurotoxicity.

g/ NA=skeletal examination was not performed.

III.G.3. Oral - Rat

Pregnant rats (Crj:CD (SD), 23-24 rats/dose) were given methyl bromide (purity 99.5%; 0, 3, 10, or 30 mg/kg) dissolved in corn oil by gavage on gestation days 6-15 and sacrificed on day 20 (Kaneda *et al.*, 1998). No clinical signs were observed. Food consumption and weight gain were reduced in the dams of the 30 mg/kg group. Food consumption was also reduced in the control group given corn oil; this suggested that the effect may be related to the large volume of corn oil used (10 mL/kg) or the method of administration. At necropsy, all dams in the 30 mg/kg group showed erosion and thickening of the wall in the nonglandular part of the stomach and adhesions between the stomach and the spleen, liver or diaphragm. In the fetuses from the 30 mg/kg dams, there were increased incidences of microphthalmia in 2 fetuses (two litters, 8% incidence), and having 25 (not 26) presacral vertebrae count in 5 fetuses (two litters, 8% incidence). While neither effect was statistically significant, no cases were observed in the control group. This study was considered supplemental information by DPR.

III.G.4. Oral - Rabbit

Pregnant rabbits (Kbl:JW, 15-18 rabbits/dose) were given methyl bromide (purity 99.5%; 0, 1, 3, or 10 mg/kg) dissolved in corn oil by gavage on gestation days 6-18 and sacrificed on day 27 (Kaneda *et al.*, 1998). No clinical signs were observed. Food consumption and weight gain were reduced in the does of the 10 mg/kg group. In the fetuses, total litter resorption occurred in 2 does of the 10 mg/kg groups and one control doe; the number of resorptions involved were not indicated. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/sternebrae; and absence of the metacarpal and phalangeal bones. While the number of fetuses with malformation were higher in the treated groups than the control groups; the increase was neither statistically significant at the litter level nor related to the dose. This study was considered supplemental information by DPR.

III.H. NEUROTOXICITY

Methyl bromide is a known neurotoxicant to both humans and experimental animals. The neurotoxicity of methyl bromide in laboratory animals was described **II.A. CHEMICAL IDENTIFICATION** and in previous sections of the **III. TOXICOLOGY PROFILE**. Delayed neurotoxicity study under the FIFRA guidelines is not currently required.

For neurotoxicity in humans, information was available primarily from accidental poisonings. The following selected reports from residential and occupational exposures were those where methyl bromide levels were available or effects adequately described.

III.H.1. Occupational Exposure

One of the earliest reports on the effects of methyl bromide from occupational exposure was those from a 2-week observation in a repackaging plant (Watrous, 1942). The workers manually filled, sealed, inspected, recovered, and packaged methyl bromide from a tank into glass ampules. It is not known whether these workers had previous exposure to methyl bromide. During the first week of the study, the workers had potentially high exposures to methyl bromide due to handling of ampules by hand, spillage during filling, inadequate hood exhaust, and two reported accidents (broken ampules from a packaged box and broken pipe from the methyl bromide tank). While gross methyl bromide leaks were detected by the flame detector, actual measurements were not recorded. In the second week, the work environment was better controlled in that ampules were held by clamps, spillage was vented, and a larger blower was installed for the hoods. Methyl bromide air concentrations were measured hourly at the breathing level of the workers by the flame detector (detection limit of 35 ppm). The recorded methyl bromide air concentration was generally less than 35 ppm. During this 2-week period, twenty-two cases of skin lesions were reported. These were attributed to direct contact of methyl bromide on the skin (i.e. from spillage) and resulted in blisters and/or dermatitis. Seventeen of these 22 cases also complained of systemic symptoms. Overall, 31 of the 90 workers in the filling and sealing rooms developed systemic effects over the 2-week period. The onset of the symptoms as to time after exposure was noted as “variable...sometimes occurring at work after a few hours exposure, and sometimes being delayed until several hours after..the shift.” The most common symptoms were anorexia and nausea with variable onset and duration. Headaches were reported to occur only during exposure and were often elicited only after specific questioning of the workers. Vertigo and faintness were reported following “known exposure.” The relationship between methyl bromide exposure and other symptoms such as sensations in the eyes, sleepiness, spigastric or substernal pain, and muscular pain were considered questionable.

An investigation was initiated in a date packing plant when 15-20 more workers were absent within a period of 2 to 10 days (Johnstone, 1945). Neurotoxicity was reported in 34 workers exposed to methyl bromide between 100 to 500 ppm for an unknown amount of time while working in the plant . Visual disturbance was present in every case and other symptoms were speech disturbance (23/34), numbness of the extremities (18/34), mental confusion (15/34), hallucination (7/34), melancholia (2/34), coma (4/34), convulsion (1/34), apathy (1/34), tremor (4/34), neurosis (3/34), and fainting attacks (3/34).

Neurobehavioral functions were evaluated in 128 California structural and soil

fumigators who had been working with methyl bromide, sulfuryl fluoride, or the combination for at least one year (Anger *et al.*, 1986). The following summary of the report describes only the results for the methyl bromide group. Exposure data for the various work activities are summarized below:

Occupation (number of workers)	Estimated Work hours/day	Exposure Mean (range) ppm	Source of Data
soil fumigator (4)	8	2.3 (0-6.2)	NIOSH
soil fumigator (30)	not given	2.6 (0-7.4)	DPR
tarp remover (4)	variable	4.5 (0-8.6)	NIOSH
shoveler (11)	variable	0.8 (0-2.3)	DPR
structural fumigator (10)	1.5	0.8 (0-2.2)	NIOSH

There was a higher prevalence of muscle aching and fatigue, increased threshold for the two-point test for finger sensitivity, and a lower number of facts recalled in the Wechsler Memory Scale for the methyl bromide group. This group also consistently showed lower performance on neuorbehavioral test measures. Mild neurologic dysfunctions were observed in some subjects; they included increased tremors, unsteadiness on standing with eyes closed, ataxia, and poor grip strength. The authors offered the following caveats for the interpretation of the results: (1) lack of information on participation rates and bias; (2) group differences in age, educational level, race, alcohol consumption, use of prescription drugs, and use of "illegal drugs"; and, (3) the possibility of over-reporting of the symptoms.

In an acute exposure, four nursery workers were exposed to methyl bromide while untarping a field (6 acres) which had been treated with methyl bromide (350 lbs/acre) and covered for 10 days (Herzstein and Cullen, 1990). None of the workers had a history of exposure to methyl bromide or had used pesticides during the 6-week period before the incident. During the days of untarping, the workers experienced fatigue and light-headedness. After work, they developed severe coughing, chest tightness, nausea, vomiting, frontal headaches, tremulousness, ataxia, and tremor. The symptoms were less severe over the next 2 to 3 weeks. By 3 weeks, two of the workers reported upper- and lower-extremity paresthesia and reduced hand dexterity. Clinical tests conducted after exposure and follow-up visits were within normal limits. No long-term adverse health effects were reported after 18 months.

In the Netherlands, 9 greenhouse workers were exposed to methyl bromide from an adjacent fumigated area via poor seals around a door and open pipes (Hustinx *et al.*, 1993). Methyl bromide used (200 g/m^2) was 5 times the legal use. Some workers were previously exposed to methyl bromide and had experienced symptoms (nausea, vomiting, dizziness, and poor memory). On the first day of fumigation, the methyl bromide level was 25 ppm in the non-fumigated side. On the second day when the workers were poisoned, the methyl bromide levels ranged from 150 to 200 ppm. All, except one worker, experienced extreme nausea, repeated vomiting, and dizziness. The other one felt only a burning sensation in the throat. Two workers later developed seizures. Others complained of headache, nausea, ataxia, slurred speech, and a sensation described as "floating." The serum bromide levels ranged from 51 to 363 mg/L and were higher than the general population. Most of the levels (5-119 mg/L) remained elevated 19 days after exposure. The severity of the symptoms did not correlate with the bromide levels, but was associated with known previous exposures to methyl bromide.

Two workers were exposed to a high concentration (4400 ppm) of methyl bromide for 45 minutes when aerating a fumigated mill (Deschamps and Turpin, 1996; Garnier *et al.*, 1996). Both experienced nausea, vomiting, headache and dizziness after exposure. Two hours later, one (44 years old) of them had severe myoclonic seizures. This worker was hospitalized and still had ataxia, debilitating action/intention myoclonus, bilateral cortical deafness, and mental deterioration upon discharge after 52 days in the hospital. One year later, the worker remained affected and was confined to a wheel chair. The second worker (39 years old) was less affected and did not develop seizures or myoclonus. One year after the accident, he showed only a mild deficit in verbal memory. Analysis of the blood collected 7 weeks after the accident showed that the difference in response between these two workers may be due to a difference in glutathione transferase level. The more severe neurotoxicity experienced by the older worker was attributed to two factors. First, glutathione transferase activity was higher in this worker (Garnier *et al.*, 1996). The formation of S-methyl-glutathione was hypothesized to be involved in the neurotoxicity observed. On the other hand, the second worker had higher levels of S-methylcysteine adducts in the erythrocyte proteins. Second, the filter mask of this individual was considered "inefficient" which resulted in a 3-fold higher blood bromide level than that for the younger worker.

In a cross-sectional study conducted in 1992 and 1993 by the National Institute for Occupational Safety and Health (NIOSH) and the University of Miami, potential chronic health effects of 123 structural fumigation workers in South Florida were evaluated (Calvert *et al.*, 1998b). A majority of the workers (112) were exposed to methyl bromide and sulfuryl fluoride, with the remaining workers exposed to sulfuryl fluoride only. The median year for employment in the structural fumigation was 4 years (range 0.5 to 32 years). The medians for years worked with methyl bromide and sulfuryl fluoride were 1.2 years (range 0-22.1 years) and 2.85 years (0.11 to 20.5 years), respectively. The tests for neurological function included those for: nerve conduction, vibration, neurobehavioral tests from the Neurobehavioral Evaluation System, vocabulary, Santa Ana Dexterity, posture, contrast sensitivity, color vision, and olfactory function. In addition, urine analysis, lung function, and physical examination were conducted. Pattern memory and olfactory function were the only tests which showed significant difference between workers with high sulfuryl fluoride exposures and the referents. Reduced performance in the Santa Ana Dexterity test by the workers was attributed to the physical damage due to the use of heavy-duty spring clamps to fasten tarps. The authors found few health effects associated with methyl bromide but noted that the study had limited power to assess the exposure.

III.H.2. Residential Exposure

A woman was exposed to methyl bromide after returning to her home which had been fumigated and cleared for reentry (Reidy *et al.*, 1994). Initially, she had trouble breathing and developed headaches, diarrhea, continued nausea, and rashes over uncovered portions of the body for 2 days. The headache continued for several months after the initial exposure. Air sampling done 9 weeks after reentry showed the highest measurements were 3 ppm in the air above the bathroom carpet pad, and 2 ppm in the air above the front door. It was determined that an excessive amount of methyl bromide was used during fumigation. The actual peak exposure on the first day of reentry was estimated to be 400 to 1500 ppm. The woman continued to live in the home for 14 weeks after the fumigation. She showed impairments in

concentration, information processing, learning, and memory as well as emotional stress in a comprehensive neuro-psychological evaluation administered a few days after she moved out of the home.

In another fumigation, a family (a couple with a 3-1/2 month old infant) was exposed to methyl bromide from a neighboring house through emptied sewage pipes (Langard *et al.*, 1996). The estimated air concentration was 6430 ppm in the fumigated house. After about 2.5 hours of exposure, the infant cried vigorously, vomited, and had severe diarrhea. The symptoms persisted until the infant died on the next day. The autopsy showed inflammation in the lungs, blood vessels, heart, and brain. The parents were also affected as they sensed burning in their eyes, throat, and mouth and vomited. However, they recovered with no apparent neurological deficits when tested about 1 week later. The bromide levels were 170 mg/L (36 hours after exposure) for the infant, and 110-130 mg/L (39 hours) for the parents.

Another fatal case of exposure through an open connection was reported in California where a fumigated room was connected to an unattached guest house via 8 uncapped electrical conduits (Swenson *et al*., 1997). The occupant of the guest house initially complained of flu-like symptoms and was found unconscious and convulsing on the next day. Blood and urine samples collected at the emergency room showed serum bromide levels of 27 mg/dL and 6.2 mg/dL, respectively. Air analysis of one adjoining tube on the 6th day after fumigation showed 15 ppm methyl bromide.

IV. RISK ASSESSMENT FOR INHALATION EXPOSURE

IV.A. HAZARD IDENTIFICATION

The most appropriate data for the hazard identification of methyl bromide are those from human studies. However, human case reports (**III.H. NEUROTOXICITY**) did not provide sufficient detail on the dose-response relationship. In the absence of human data, results from animal studies were extrapolated to humans assuming that the effects observed in laboratory animals would also be observed in humans. Toxicity endpoints and critical NOELs for risk characterization are discussed in this section (details of the studies are in **III. TOXICOLOGY PROFILE**). The no-effect levels may be expressed in terms of NOAELs or NOELs. Only those endpoints considered of toxicological significance were used for risk characterization.

The study to evaluate the chronic inhalation toxicity of methyl bromide in a nonrodent species (*i.e*. dogs), as part of the SB 950 data requirement, has not been submitted to DPR. While a chronic inhalation study in the dog would further characterize the neurotoxicity of methyl bromide, the requirement was waived by DPR based on the evaluation of short-term studies in the dog (Newton, 1994 a and b) which showed that a chronic study would have to be conducted at relatively low dose levels (Oshima, 1995; Gee, 1995). These levels would be in the range of the estimated NOELs from the rat (Reuzel *et al.*, 1987 and 1991) and mouse oncogenicity studies (NTP, 1992; Eustis, 1992). The chronic inhalation study would be required by DPR if the basis for the waiver is changed.

IV.A.1. Selection of Toxicity Endpoints

The selection of a toxicity endpoint and its associated NOEL involved the review of the published literature and registrant-submitted studies for the most appropriate endpoint to assess human exposure. The NRC in the review of the draft RCD/1999 agreed with DPR selection of endpoints for risk characterization (NRC, 2000).

IV.A.1.a. Developmental Toxicity

One endpoint DPR considered for risk assessment is the development toxicity observed in experimental animals after methyl bromide exposure. In a developmental toxicity study, the pregnant animals are exposed continuously to methyl bromide during a specified period of gestation (when organ formation occurs). Any adverse effect observed in the fetus is considered an acute effect under the current assumption that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. Environmental Protection Agency Guidelines for Developmental Toxicity Risk Assessment. Since this endpoint is the result of exposure during pregnancy, it is only used for the assessment of exposure by women of childbearing age.

The critical NOEL for developmental toxicity was 40 ppm from a study with rabbits. The result from this study was the basis for the emergency regulation and permit conditions currently used in California. U.S. EPA also considered these endpoints of concern and has used the same study in a Section 18 evaluation on the use of methyl bromide on imported fruits at ports of entry. In this rabbit developmental toxicity study, fetuses exposed to 80 ppm *in utero* showed gall bladder agenesis (no gall bladders), fused sternebrae (early fusion of the

sternebrae), and lowered body weights. The missing gallbladder finding was seen in Part I of the experiment, which by itself is a complete study and fulfilled FIFRA guidelines for an acceptable study. The investigator was concerned with the finding as it was rarely observed in the negative-control litters in the conducting laboratory as well as in other laboratories using the same rabbit strain. When the experiment (Part II) was repeated three months later, missing gall bladders were again observed in fetuses exposed to methyl bromide *in utero*. The fused sternebrae found in Part I was not confirmed since skeletal examination was not performed in Part II.

The developmental toxicity effects observed in fetuses should not be discounted because of maternal toxicity (body weight changes and neurotoxicity) reported at the same dose level. Consideration must be given to when the effects were observed. First, the decrease in the body weight gain of the 80 ppm group does was not a consistent finding. Statistically significant decreases were reported for gestation days 13-16 in Part I and gestation days 7-20 and 10-13 periods in Part II. The reduced weight gain in the does of Part II occurred concomitantly with a reduction in the mean fetal body weight. Second, there was no significant difference in the strictly maternal parameter calculated as the terminal body weight minus gravid uterine weight. Third, body weight changes in pregnant rabbits are known to be more variable than rodents. As a result, body weight changes in rabbits often do not carry as much weight as an indicator for maternal toxicity as for rodents as discussed in the U.S. EPA Developmental Toxicity Risk Assessment guidelines. Fourth, maternal neurotoxicity was characterized by clinical signs; including lethargy, head tilt, slight ataxia and slight lateral recumbency. These signs were observed in only 3 of 43 does (7%) dosed at 80 ppm and they did not appear until gestation days 19-20 (the last days of the 13-day exposure period). Based on the description and comparison with observations reported in other studies, DPR did not consider these signs as indicators of excessive toxicity.

Furthermore, the failure of gall bladders to form in some fetuses was independent of maternal neurotoxicity. In Part I, 6 of the fetuses with missing gallbladders were from 3 does without neurotoxicity while the remaining 7 affected fetuses were from 2 does with neurotoxicity. In Part II, none of the does showed neurotoxicity while 4 fetuses (from 4 does) had missing gallbladders. In addition, the development of the gall bladder in rabbits can be considered an acute event since it takes place in one to two days after its onset on gestation day 11.5 (Hoar and Monie, 1981). The maternal neurotoxicity reported on gestation days 19-20 would have occurred too late to have been a factor in the agenesis of the gall bladder.

Similar findings have not been reported in the rat developmental toxicity studies. While it it worth noting that rats do not have gall bladders, the absence of these findings in another species should not negate their significance as indicators of the potential for methyl bromide to cause developmental toxicity in humans. Species specificity in developmental effects has been demonstrated for some chemicals. Developmental toxicity testing under the FIFRA guidelines requires two species to be tested, a rodent and a non-rodent species, typically the rabbit, for the purpose of identifying species susceptibility. The need to test non-rodent species arose from the findings of thalidomide where it was demonstrated that this human teratogen did not exhibit significant teratological effects in rats but caused at least some significant effects in rabbits (Schardein, 1985). As stated in the U.S. EPA Developmental Toxicity Risk Assessment guidelines, developmental effects may not be evident in more than one species. The findings from the most sensitive species are appropriate to use to estimate human risk.

The significance of the developmental toxicity findings was discussed in a 1994 Proposition 65 meeting to determine whether methyl bromide should be listed for all uses. The emergency regulation in 1992 resulted in methyl bromide being listed as a chemical known to the state to be a reproductive toxicant for structural fumigation use only. The Developmental and Reproductive Toxicity Identification (DART) Committee was presented with results from animal developmental toxicity (absence of gall bladders and fused sternebrae) and reproductive toxicity (decreased pup body weight) studies. After much discussion, the Committee voted not to expand the listing of methyl bromide from structural fumigation to all uses because there was not enough evidence to support the "clearly shown" criteria as mandated by the Proposition. However, the members expressed several concerns: the need for more experimental studies to clarify the findings, potential for exposure to methyl bromide via the milk during lactation, and the lack of information on human exposure especially during pregnancy.

After this meeting, DPR received additional data to support the consideration of reproductive or developmental toxicity as a pertinent endpoint for risk assessment and regulatory actions. First, supplemental data on the rat reproductive toxicity study showed that methyl bromide caused a reduction in the width of a certain part of the brain (cerebral cortex) in the F_1 adults exposed to methyl bromide *in utero* (American Biogenics Corp., 1986). Second, a study received by DPR in 1998 showed that methyl bromide caused a breakage of DNA in the testicular cells isolated from rats after inhalation exposure (Bentley, 1994). It is not known whether the effect was due to methyl bromide or a metabolite.

In the review of the draft RCD/1999, the NRC concluded that methyl bromide may be a developmental and possibly a reproductive toxicant (NRC, 2000). The NRC also agreed with the DPR rationale for the selection of developmental toxicity as an endpoint for acute toxicity. This use could be considered a conservative approach but justifiable in the absence of data which show that gall bladder agenesis requires multiple days of exposure.

IV.A.1.b. Neurotoxicity

Methyl bromide caused neurotoxicity in all animal species studied. There are four aspects to the methyl bromide-induced neurotoxicity: (1) species sensitivity, (2) exposure duration dependency, (3) persistency of effects, and (4) cumulative toxicity.

Of the laboratory animals studied, there was a species sensitivity to the neurotoxicity of methyl bromide after short-term exposure. Based on the comparisons of the lowest-observed effect level (LOEL) for neurotoxicity, the dog and rabbit showed greater sensitivity than the guinea pig, mouse and rat. For example, dogs exposed to 156 ppm (human equivalent level of 68 ppm) showed severe neurological effects in 2 to 7 days of exposure while rats exposed to the same concentration in terms of human equivalent level (65 ppm; 70 ppm actual air concentration) for the same exposure duration did not show any neurotoxicity. In pregnant animals, the rabbit was more sensitive to methyl bromide than the rat. For pregnant rabbits, severe neurotoxicity was observed at the LOEL of 70 ppm (Sikov *et al.*, 1981; Breslin *et al.*, 1990) while no neurotoxicity was reported in the pregnant rats at the same level (Sikov *et al.*, 1981).

Although the dog inhalation toxicity studies were not designed to be one of the FIFRA guideline study types, they were conducted under Good Laboratory Practices and DPR

considered the results valid for hazard identification. These same data were used by the MBIP to support their position that a chronic inhalation toxicity study in the dog should not be required (CMA, 1994). The selection of results from the most sensitive species based on the review of the database, in this case the dog, is consistent with the U.S. EPA Neurotoxicity Risk Assessment guidelines (U.S. EPA, 1998a).

Methyl bromide-induced neurotoxicity was dependent on the dose and duration of exposure. As shown in Tables 1 and 3, there was a relatively steep dose-response relationship. The data which best illustrate this point are the results from the dog studies (Newton, 1994 a and b). No effects were observed at 103 ppm (NOEL) for up to 5 days of exposure. However, lacrimation was noted on the first day when the concentration was increased to 156 ppm (1.5 times the NOEL), and the dogs had to be sacrificed after day 6 due to neurotoxic effects. At 314 ppm (3 times the NOEL), tremors and hunched appearance were observed in both dogs after only 7 hours of exposure.

Another aspect of the methyl bromide-induced neurotoxicity is the persistence of the effect after the termination of exposure. In the NTP study, mice were treated with methyl bromide at 100 ppm (NTP, 1992). The exposure was stopped after 20 weeks because of neurotoxicity (tremors, paralysis, and other signs) and mortality. However, neurotoxicity continued to be observed in the survivors for the remainder of the 2-year study. In some cases, the first signs of neurotoxicity appeared one month or more after the last exposure to methyl bromide. Also, at the terminal sacrifice (84 weeks after the last exposure), brain lesions were found in some 100 ppm survivors suggesting that these lesions, which may have been induced during exposure, were not repaired. In rabbits, the neurotoxicity observed was shown to be associated with lesions in the midbrain and meninges (Breslin *et al.,* 1990a). Another example of persistence of effect is the neurotoxicity observed in dogs (Newton, 1994b) and in rabbits after the last exposure to methyl bromide (Sikov *et al.*, 1981).

The persistence of effect may be due to cumulative toxicity after repeated exposure to low doses. In dogs, a comparison of the clinical signs showed that the 158 ppm group was more affected than the 156 ppm by methyl bromide exposure (Newton, 1994 a and b). Decreased activity was noted in the second day (<14 total hours; hourly observations not available) of exposure to 158 ppm compared to the third day (17 total hours) for 156 ppm. The 158 ppm group was previously exposed to 11 ppm for 24 days and appeared normal during the exposure. In a study of California structural and soil fumigators working at air concentration of less than 5 ppm methyl bromide for at least one year, the workers showed lower performance on neuorbehavioral test measures and some also showed mild neurological dysfunctions (Anger *et al.*, 1986).

IV.A.1.c. Brain Monoamines and Enzyme Activity

Methyl bromide was shown to decrease tyrosine hydroxylase activity in the rat brain after acute exposure (Honma *et al.,* 1991). This decreased activity was hypothesized by the authors to be due to methyl bromide-induced structural changes to the enzyme. This endpoint and a NOEL of 16 ppm were used by the ATSDR to establish the minimum risk levels for methyl bromide (ATSDR, 1992 and 1996). The intent of the MRL was to raise concerns for additional studies rather than for regulatory action.

DPR determined that the LOELs were 16 ppm and 63 ppm based on *in vitro* and *in vivo* assay methods, respectively, for reduced tyrosine hydroxylase activity in the brain segments. It was not possible to determine which LOEL was valid since the publication was incomplete in explaining how important parts of the study were conducted.

Furthermore, the proposed hypothesis was not well substantiated by the investigators. First, there were other plausible explanations for the decreased tyrosine hydroxylase activity in the assays besides direct effects on the enzyme. Second, a decrease in tyrosine hydroxylase activity should result in a decrease in dopamine, the next metabolite in the pathway after DOPA. However, studies done earlier by Dr. Honma's group (Honma *et al.*, 1982 and 1987) either indicated that brain dopamine was not affected or that it was decreased only after levels of its catabolite, homovanillic acid, had increased. Third, the subsequent research in Dr. Honma's group (Honma *et al.*, 1994) did not corroborate or extend the findings of the 1991 paper (Honma *et al.*, 1991). More studies are needed that show the effects on tyrosine hydroxylase and brain dopamine are reproducible. Therefore, the effect of methyl bromide on tyrosine hydroxylase and catecholamines was not selected by DPR as the critical endpoint at this time. While the effect of methyl bromide on tyrosine hydroxylase, by itself, is not considered an adverse effect, the effect on catecholamines in more than one region of the brain (Table 2) was a significant finding for the consideration of critical NOELs for risk characterization. The NRC agreed with the DPR conclusion that the Honma *et al.* studies were not suitable for use in risk characterization (NRC, 2000).

IV.A.1.d. Nasal Cavity Toxicity

Another important toxicity endpoint is the methyl bromide-induced damage to the olfactory epithelium of rats and mice after inhalation exposure (Reuzel *et al.*, 1987 and 1991; NTP, 1992). This endpoint is used by the U.S. EPA in the determination of the chronic reference inhalation concentration (RfC) (U.S. EPA 1992a) and by the Office of Environmental Health and Hazards Assessment (OEHHA) for chronic toxicity reference exposure levels (RELs) (OEHHA, 1996). With acute exposure to 200 ppm, the damage to the rat olfactory epithelium included epithelial disruption, fragmentation, and exfoliation (Hurtt *et al.*, 1988). Repair of the epithelium included replacement by a squamous epithelium, loss of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). In other short-term studies, the damage to the nasal epithelium was described as necrosis and degeneration (Eustis *et al.*, 1988) and dysplasia (NTP, 1992; Eustis, 1992). In the chronic inhalation toxicity study, basal cell hyperplasia and degeneration in the olfactory epithelium were observed in the rat (Reuzel *et al*., 1987 and 1991).

While the effect on the nasal cavity may generally be considered a finding limited to the rat due to anatomical considerations, it is not the case with methyl bromide. Dogs exposed to 156 ppm methyl bromide for only 6 days showed moderate to moderately severe olfactory degeneration (Newton, 1994b). Boorman *et al.* (1990) suggested that the specificity for the toxicity of methyl bromide to this region was due to an abundance of endoplasmic reticula with high metabolic (biotransformation) activity. The greater susceptibility of the olfactory epithelium to pyridine-induced lesions has also been attributed to metabolic activation at this site (Nikula and Lewis, 1994). Air flow to this area, which amounts to 8 to12% of inspired air (Morris *et al.*, 1993; Kimbell *et al.*, 1993), was considered too slow to be a factor as a target site.

Epithelial hyperplasia of the basal cell layer observed in rats and mice may be a regenerative response or an early indication of neoplasia (Boorman *et al.*, 1990). The olfactory epithelium has remarkable regenerative capacity with a turnover time of 28 days. The basal cells are the stem cells for olfactory neurons. If the basal cells are destroyed, then olfactory epithelium cannot be reconstituted and olfactory function is impaired or lost. The regenerative ability of the basal cells does decline with age (Hastings, 1990). As part of the reparative process, prolonged injury may result in squamous metaplasia and respiratory metaplasia. Squamous metaplasia is characterized by multiple layers of epithelial cells with eosinophilic cytoplasm (Boorman *et al.*, 1990; Haschek and Witschi, 1991). Squamous cell neoplasms have been shown to develop from areas of squamous metaplasia in the olfactory epithelium (Boorman *et al.*, 1990). Respiratory metaplasia, the conversion of olfactory epithelium to a ciliated respiratory type, after exposure to methyl bromide indicates a permanent change in the cell type (Hurtt *et al.*, 1988; NTP, 1992; Eustis, 1992). Olfactory epithelial reconstitution after methyl bromide exposure has been used as the model to study the mechanism of recovery of the olfactory system (Schwob *et al.*, 1995 and 1999).

The nasal effects represented the most sensitive endpoint for chronic exposure. In the rat, lesions in the heart, and decreased brain weights were observed at higher concentrations than that for nasal effects (Table 8). In the mice, the no-effect levels were the same for nasal cavity, brain, sternum, and heart lesions (Table 11).

IV.A.2. Selection of Critical No-Observed-Effect Level

Humans are exposed to methyl bromide by inhalation (occupational, residential, and ambient air) and by oral (dietary) routes. In the evaluation of the potential effects after exposure to methyl bromide, route-specific critical NOELs were derived because the toxicity and pharmacokinetics are different between inhalation and oral exposures. After oral administration, liver and kidneys were the major organs of deposition, and there was reabsorption of biliary metabolites and/or reaction products from the gut. Toxicity was limited to the stomach and forestomach in the rat. For inhalation, the effects were systemic and involved several organs including the nasal cavity, brain, and heart. The primary routes of excretion were via the exhaled air (50% of the dose) as $^{14}CO_2$ for inhalation and intraperitoneal routes, and the urine (43% of the dose) for oral routes of administration. The NRC in the review of the draft RCD/1999 agreed with DPR on the selection of NOELs for risk characterization (NRC, 2000).

IV.A.2.a. Acute Toxicity- Inhalation

Studies with animals showed that there is a relatively steep dose-response relationship in which the difference between 100% survival and 100% mortality was only a 2- to 10-fold increase in concentration. The sublethal effects of methyl bromide included neurotoxicity, biochemical alterations, and tissue degeneration (Table 5).

The critical NOEL for acute exposure was selected from neurotoxicity and developmental toxicity studies. For the adult population, especially for women of childbearing age, the lowest NOEL was from the rabbit developmental study by Breslin *et al.* (1990b) since the dosage was lower than that used in the rat study (Sikov *et al.*, 1981). Even though in the developmental study the exposure was repeated during the gestation period, the primary

assumption is that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991).

In the rabbit developmental study, the NOEL was 40 ppm (human/adult equivalent of 21 ppm) (Breslin *et al.*, 1990b). Fetal malformations (omphalocele, retro-esophageal right subclavian artery, and gall bladder agenesis), variations (fused sternebrae), and decreased fetal body weights were observed in the fetuses of does exposed to methyl bromide at 80 ppm. Since these malformations are rarely seen in litters of untreated rabbits, they were considered treatment-induced in this study. The occurrence of these effects in a single group by chance was unlikely given the historical control data for the conducting laboratory (for more discussion, see Attachment B). The increased incidences of gall bladder agenesis and fused sternebrae were statistically significant ($p \leq 0.05$) (Table 17). Furthermore, gall bladder agenesis was confirmed when the experiment was repeated. Skeletal examinations were not done in the second experiment. Both adverse effects were observed in fetuses from does with and without neurotoxicity, indicating that maternal toxicity was unlikely to be the determining factor in the development of the defects.

Developmental effects were also observed in the rat, though to a lesser extent compared to the rabbit. In rats, the fetuses of the two groups exposed to 70 ppm methyl bromide showed increased delayed skull ossification, and the NOEL was 20 ppm (human/adult equivalent NOEL of 22 ppm) (Sikov *et al.*, 1981). No maternal toxicity was observed in this study.

For other population groups, including infants and children, the most appropriate endpoint for risk assessment is neurotoxicity. The lowest NOEL was <16 ppm (human/child equivalent of <11 ppm) for a decrease in tyrosine hydroxylase activity in the rat hypothalamus (Honma *et al.*, 1987 and 1991). This NOEL from the *in vitro* assay was not selected for risk assessment because of the inconsistencies in the findings and interpretation of the results (**IV.A.1.b. Brain Monoamines and Enzyme Activity)**. However, the NOEL (31 ppm or human/child equivalent of 22 ppm) for altered catecholamines in more than one region of the brain was considered as a support for the critical NOEL derived from the dog studies.

The critical acute NOELs for neurotoxicity were considered from clinical observations in dogs (Table 4; Newton, 1994 a and b). The selection of the 103 ppm dose (human/child equivalent of 25 ppm) as the acute NOEL considered three major factors: subjectiveness of the observations, severity of the neurotoxicity at higher concentrations, and possibility of delayed neurotoxicity. The NOEL of 103 ppm in the dogs was based on gross observations. Neurotoxicity may be present but not detected unless more refined methods such as the Functional Observation Battery were used. It is possible that the actual NOEL may be lower than 103 ppm. Furthermore, severe neurotoxicity was observed at higher doses (1.5 times the NOEL) with a few additional days of exposure. At 156 ppm, one of two dogs showed lacrimation (tearing) on the first day. This finding by itself may arguably be considered less significant with respect to adversity. However, there were only two dogs in this group. With 2-3 days of additional exposure, both dogs showed significant toxicity manifested as difficulty in breathing and decreased activity. In another study, all dogs (8 in the group) exposed to 158 ppm showed decreased activity before the end of the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). With 5 additional days of

exposure, all showed severe neurotoxicity and brain lesions. The selection of 103 ppm as the acute NOEL also addresses, indirectly, the possibility of delayed neurotoxicity which has been reported in humans after accidental poisonings. Since no effects were observed in the dogs at 103 ppm for 7 days of continuous exposure, it is unlikely that there would be delayed neurotoxicity within one week after a single exposure to the same level. The human equivalent NOEL (25 ppm) from the dog study is only two-fold or less than those for the acute effects observed in the rats and guinea pigs (Table 7).

From the two critical acute NOELs selected to address human population groups, the critical NOEL of 40 ppm (human/adult equivalent of 21 ppm) for developmental toxicity in the rabbit was most appropriate for workers and residents since women of child bearing age are in both groups. For children, the critical NOEL was 103 ppm (human/child equivalent of 25 ppm) for neurotoxicity in the dog (Newton, 1994a). Since the developmental toxicity NOEL was lower than that for neurotoxicity, this NOEL was selected for risk characterization to address occupational and residential exposures and would also be protective of the children population.

IV.A.2.b. Subchronic Toxicity- Inhalation

From occupational and residential uses of methyl bromide, there is a potential for subchronic inhalation toxicity from short-term exposure periods due to a single application, and from multiple applications during a season. One example of potential short-term exposure is from the release of methyl bromide from wall space of fumigated homes. Current label allows residents to reenter treated homes when the methyl bromide concentration reached $\leq$1 ppm in the wall space. Residents living next to fumigation chambers or fields with consecutive application may also experience short-term exposures.

For continuous exposure of 1 week, methyl bromide effects on the brain and clinical signs of neurotoxicity were the endpoints used to select the critical NOEL (Table 7). For this duration of exposure, the lowest and the critical NOEL was 20 ppm (human/child equivalent of 7 ppm) for neurotoxicity and death in pregnant rabbits (Sikov *et al.*, 1981). After approximately 1 week (exact number of days not reported), the 70 ppm does showed a decrease in body weight and signs of neurotoxicity (convulsive movements, severe to partial paresis of the hind limb). One of 26 does died on gestation day 9, and two more does died on gestation day 10. Though dosing stopped on gestation day 15, all but one of the 70 ppm does were dead by gestation day 30. Neurotoxicity was also observed in pregnant rabbits in two other studies (Breslin *et al.*, 1990 a and b). The NOELs (70 ppm and 40 ppm) were higher in these latter studies compared to that from Sikov *et al.* (1981). The lower NOEL from the Sikov *et al.* (1981) study may be due to longer exposure as the rabbits were exposed earlier (gestation day 1 compared to gestation day 7) and longer each day (7 hours instead of 6 hours).

The NOEL of 26 ppm (human/child equivalent of 5 ppm) for decreased activity in the dog after 14 days of exposure to 53 ppm was also considered for the short-term critical NOEL. The decreased activity was considered an early sign of neurotoxicity since decreased activity and more severe signs of neurotoxicity were observed in the 103 ppm group during the 1-2 weeks of exposure. However, the time to effect (14 days) was much longer than the duration (7 days) for the scenarios of concern.

For subchronic exposures of longer duration (90 days, seasonal), the critical NOEL was

an estimated NOEL (ENEL) of 0.5 ppm (human/child equivalent of 0.1 ppm) based on a LOAEL of 5 ppm for decreased responsiveness in two of eight dogs during a neurological examination after 6 weeks of exposure (30 exposure days). A default uncertainty factor of 10 was used to calculate the NOEL from a LOAEL (Dourson and Stara, 1983). While the duration is shorter than the 13-week generally considered for subchronic exposure, it was chosen because of the endpoint (neurotoxicity) and species sensitivity (the dog is a more sensitive species than the rat to methyl bromide). It is possible that the NOEL might be lower if the dogs were exposed to methyl bromide for 13 weeks. The NRC considered this NOEL as conservative and the endpoint to be equivocal because of the lack of a dose-response curve, non-standard testing protocol, and low number of replications (NRC, 2000). However, the NRC concluded that the endpoint was reasonable because of neurotoxicity concerns and the use of this NOEL would probably be protective even for longer exposure durations.

This ENEL (child equivalent of 0.1 ppm) was lower than the NOEL (3 ppm, human/adult equivalent of 2 ppm) for lowered body weights of rat pups from dams exposed to methyl bromide before mating and during part of the pregnancy in the reproductive toxicity study (American Biogenics Corp., 1986) (Table 16). The reduction of pup body weight was both dose- and time- dependent with respect to the adult exposure, with the highest reduction occurring in the F2b 30 ppm and 90 ppm litters. There was also decreased brain weight in the F_1 adults at 30 ppm. This study and the endpoint are appropriate to evaluate the potential effects in humans exposed to methyl bromide during pregnancy. The potential post-natal toxicity was, therefore, accounted for by the use of the lower ENEL for neurotoxicity in the dog. Another study also showed an estimated NOEL of 3 ppm (human/child equivalent of 1.1 ppm) based on a significant decrease in the absolute brain weight in female rats exposed to 30 ppm and higher concentrations of methyl bromide for 13 weeks (Norris *et al*., 1993 a and b). This effect on the brain weight was considered biologically significant since the brain is a target organ of methyl bromide. The absence of neurotoxicity by Functional Observation Battery testing at the same dose (30 ppm) does not diminish the importance of the brain weight finding since the etiology of the two effects are not necessarily related.

IV.A.2.c. Chronic Toxicity- Inhalation

For chronic inhalation exposure, all chronic studies conducted with rodents (rats and mice), the reproductive toxicity study, and the subchronic dog inhalation toxicity study were considered in the determination of the chronic critical NOEL. While the exposure duration in chronic toxicity studies generally lasted for the life-time for rodents, the actual duration of the testing was two years. Since humans may be exposed to methyl bromide on a yearly basis, not just one or two years in the lifetime, the NOEL from the chronic toxicity study after two years of exposure was, therefore, appropriate for use. This NOEL may underestimate the risk of repeated yearly exposure as there is evidence of cumulative toxicity for this endpoint, as well as for neurotoxicity.

After chronic inhalation exposure, tissue damage was noted in the nasal cavity, brain, and heart of rodents. The most significant finding after chronic exposure was the dose-dependent increase in the incidences of nasal olfactory epithelial hyperplasia and respiration metaplasia found in rodents (Reuzel *et al.*, 1987 and 1991; NTP, 1991; Eustis, 1992; Gotoh *et al.*, 1994). In the Reuzel *et al.* study (1987 and 1991), the incidences of hyperplasia were dependent on the exposure duration as there was an increase in the number of rats affected

from 1 year to 2.5 years of exposure. The LOAELs were >90 ppm, 30 ppm, and 3 ppm for exposures lasting 12 months, 12-24 months, and 24-29 months, respectively (Table 8). At 30 ppm, there was also a reduction of absolute brain weight with a NOEL of 3 ppm. Using a standard default uncertainty factor of 10 for the calculation of an estimated NOEL from the LOEL (Dourson and Stara, 1983) for the 24-29 months of exposure, the critical ENEL for basal cell hyperplasia/ degeneration in the rat olfactory epithelium was 0.3 ppm (human/child equivalent of 0.1 ppm).

The LOAEL of 3 ppm from the rat inhalation study by Reuzel *et al*. (1987 and 1991) was supported by the study of Gotoh *et al*. (1994). In the Gotoh *et al.* study, the estimated NOEL was 4 ppm (human/child equivalent of 0.1 ppm) for nasal cavity inflammation ($\geq$ 4ppm males) and respiratory metaplasia (4 ppm females) in rats exposed to methyl bromide by inhalation for 104 weeks. Other long-term studies showed higher NOELs or ENELs than the critical ENEL. In the mouse chronic toxicity study, the LOEL was 10 ppm for neurobehavioral effects and sternal dysplasia (NTP, 1992; Eustis, 1992). Using a default uncertainty factor of 10 for the calculation of a NOEL from a LOEL, the ENEL would be 1 ppm (human/adult equivalent of 0.7 ppm). In the reproductive toxicity study, pregnant rats showed a reduction in fertility indices (American Biogenics Corp., 1986). However, the NOEL of 3 ppm (human equivalent of 2 ppm) was higher than the 0.3 ppm ENEL for olfactory epithelial hyperplasia observed in the rat oncogenicity study (Reuzel *et al.*, 1987 and 1991).

Another comparison of the NOELs was made with the results from the subchronic neurotoxicity study. The ENEL of 0.3 ppm for nasal cavity effects when expressed as human/child equivalent level (0.1 ppm) was the same as the human equivalent level for neurotoxicity after subchronic exposure (ENEL of 0.5 ppm). This implied that the actual NOEL for chronic exposure if based on neurotoxicity could be lower than that based on the effects in the nasal cavity. However, it is not possible to extrapolate such a NOEL at this time because the subchronic ENEL was already an estimated NOEL based on a LOEL which was reduced by a 10-fold uncertainty factor. The use of two 10-fold uncertainty factors to the subchronic LOEL may result in a no-effect level well below the threshold for neurotoxicity after chronic exposure.

IV.A.2.d. Oncogenicity

The genotoxicity studies showed that methyl bromide is a direct-acting mutagen. It has been shown to alkylate DNA in different organs in *in vivo* studies (Djalali-Behzad *et al.*, 1981; Gansewendt *et al.*, 1991) and was positive for genotoxicity in several *in vitro* and *in vivo* assays (Table 15). A recent report showed genotoxicity in workers exposed to methyl bromide (Calvert *et al.*, 1998). In addition, methyl bromide belongs to the methyl halide group (methylating agents) which includes methyl chloride and methyl iodide. These chemicals have been shown to be genotoxic in *in vitro* assays and do not require exogenous metabolic activation systems (Bolt and Gansewendt, 1993).

While the positive findings in genotoxicity studies suggest that methyl bromide is potentially oncogenic, the current toxicology database did not provide clear evidence of oncogenicity for methyl bromide. After chronic inhalation exposure to methyl bromide, dose-related responses were identified only for non-neoplastic lesions and included nasal epithelial hyperplasia in Wistar rats (Reuzel *et al.*, 1987 and 1991) and B6C3F1 mice (NTP, 1992; Eustis, 1992). Other studies showed various tumors but were limited to some dose groups or low

incidences. Adrenal gland pheochromocytoma in Fischer rats and lymphoma in BDF1 mice (Gotoh *et al.,* 1994) and glioma and granular cell myoblastoma in Wistar rats (Reuzel *et al.,* 1987 and 1991) were reported in the low dose female group only. In a chronic oral study with rats using methyl bromide microcapsules mixed in the feed, various tumors detected were lymphoma (males only, low dose groups only at 3-4%), prostate adenocarcinoma (high dose male at 4%) and cervical endometrial stromal sarcoma (high dose female at 4%). It should be noted that these tumor incidences for this study are not overall incidences for the study. While histological examinations of organs were performed on all rats of the control and high dose groups, they were conducted only on those rats that did not survive to the end of the study for the other dose groups. In a subchronic study, an early squamous cell carcinoma in the forestomach was detected in one animal after gavage treatment (only one dose tested) for 25 weeks (Boorman *et al.*, 1986). Since methyl bromide is a known irritant and hyperplasia of the forestomach epithelium was observed throughout the experiment, the carcinoma could be due to a direct contact effect.

In addition to genotoxicity, methyl bromide is expected to be oncogenic because chemicals of similar structures, such as methyl chloride and methyl iodide, are oncogenic in experimental animals (Bolt and Gansewendt, 1993). Methyl chloride induced renal tumors in male mice but not in rats after inhalation exposures. Methyl iodide caused lung adenomas in mice after intraperitoneal administration and local sarcomas after subcutaneous injection. The difference in the tumor sites suggests that different mechanisms for oncogenicity for these two chemicals. The lack of oncogenicity in the experimental studies with methyl bromide may be related to the exposure duration and cellular response to the genotoxic effects. In studies comparing the incidence of sister chromatid exchanges in the bone marrow between after 10 exposure days and 12 weeks at similar concentrations of methyl bromide, there was a decrease in response in the 12 week experiment (NTP, 1992). The author suggested that the lower response may be due to changes in metabolism or sensitivity of the bone marrow cells from prolonged exposure. This possibility may explain why there is no oncogenicity observed in the chronic toxicity studies where the doses used were similar to those used in the genotoxicity studies (noting that different strains were used). In the rat (Wistar rats) chronic toxicity study, the highest dose tested was 90 ppm without any evidence of oncogenicity (Reuzel *et al.*, 1987, 1991). In comparison, male rats (F-344) exposed to 131 ppm after a single 6 hours of exposure showed DNA adducts in various tissues (Gansewendt *et al.*, 1991). For mice, the highest dose in the oncogenicity study was 33 ppm for 2 years and without any tumors (B6C3F1 mice: NTP, 1992) compared with 36 ppm for 4 hours resulting in DNA adducts in the liver and spleen (CBA mice; Djalali-Behzad *et al.*, 1981). Another possibility is that the DNA adduct levels were below the threshold required for mutagenesis and oncogenesis. In the studies by Pletsa *et al.* (1999), the presence of O^6-methylguanine adducts were detected in several tissues of Sprague-Dawley rats and lamda lacZ transgenic mice after exposure to methyl bromide. The multiple dosing regiment also resulted in a decrease of O^6-alkylguanine-DNA alkyltransferase, a repair enzyme, in the tissues examined. However, the presence of these adducts did not lead to increased mutation frequency. The hypothesis was that the adduct levels were at pre-mutagenic level and that other events, such as cell proliferation, also need to be activated for mutagenesis to occur.

Therefore, the oncogenic risk for methyl bromide was not considered based on the currently available data. The NRC agreed with the DPR conclusion that the current database did not show methyl bromide to be oncogenic (NRC, 2000). Another concern on the

oncogenicity of methyl bromide is the possibility that certain people in the population with genetic polymorphism for glutathione-S-transferase may be more susceptible than others to the oncogenicity of methyl bromide. A discussion on this topic is included in **V.D.2. Intraspecies Extrapolation**.

A summary of the critical NOELs for risk characterization is presented in Table 18.

Table 18. The critical no-observed-effects levels (NOELs) for the risk characterization of inhalation exposures to methyl bromide.

Scenarios	Experimental NOEL	Human Equivalent NOEL[a]		Reference Concentration[d]	Effects in Animal Studies	Ref[e]
		Adult[b]	Child[c]			
Acute	40 ppm	21 ppm	na	210 ppb	Developmental toxicity (pregnant rabbit)	1*
	103 ppm[f]	45 ppm	25 ppm		Neurotoxicity (dog)	2
Subchronic 1 week	20 ppm	12 ppm	7 ppm	120 ppb(adult) 70 ppb (child)	Neurotoxicity (pregnant rabbit)	3
6 weeks	0.5 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Neurotoxicity (dog)	2
Chronic	0.3 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Nasal epithelial hyperplasia/ degeneration (rat)	4*

a/ Experimental NOELs were converted to human equivalents using equations in Attachment G. na= child equivalent NOEL were not calculated because the effects were observed in pregnant animals.

b/ The adult equivalent NOELs are appropriate to address worker exposures. They are also used for residential exposures when child equivalent NOELs were not calculated.

c/ The child equivalent NOELs are appropriate to address resident exposures (see footnote b).

d/ The reference concentration is the ratio of the human equivalent NOEL and a default uncertainty factor of 100 since the NOEL was derived from experimental animal studies.

e/ * indicates study was acceptable to DPR according to FIFRA guidelines. References: 1. Breslin *et al.*, 1990b; 2. Newton, 1994b; 3. Sikov *et al.*, 1981; 4. Reuzel *et al.*, 1987 and 1991.

f/ The NOEL and human equivalents are presented in this Table for comparison purposes only. They are not used for risk characterization.

IV.B. INHALATION EXPOSURE ASSESSMENT

Human exposure assessment was conducted for occupational and residential inhalation exposures to methyl bromide (Tables 19-23 based on Attachments F, H, and references within). This assessment addressed only exposure scenarios where there were available data or when the exposure could be estimated based on DPR permit conditions or regulations (referred to as DPR regulations[7]). The exposure levels were expressed as methyl bromide concentration in the air (ppb). Exposure durations considered were: acute (daily exposure), short-term (referred to as 7 day or subacute in Attachment F), subchronic, and chronic (annual) exposures. All exposure estimates based on monitoring studies were adjusted for 50% recovery (discussed in Attachment F). Dermal exposure was not considered because published studies showed that dermal exposure was significant at much higher methyl bromide air concentration than those estimated from occupational and residential exposures (Attachment F). Skin lesions were observed in workers exposed to high concentrations of methyl bromide (Zwaveling *et al.*, 1987; Hezemans-Boer, 1988; Lifshitz and Gavrilov, 2000). There are no data on the dermal absorption of methyl bromide.

Compared to the draft RCD/1999, this exposure assessment was revised to incorporate some of the NRC recommendations (NRC, 2000) as well as other changes needed (Specific details are provided under **IV.B.1.** and **IV.B.2.**). The NRC recommended collection of additional data to better characterize the exposures of workers and residents. Due to limited resources, DPR focused on residential exposure and collected ambient monitoring data for three California counties. These additional data were incorporated in this assessment (**IV.B.1.**). No additional worker exposure data were collected by DPR or submitted by the registrant. The NRC recommended re-analysis of the worker and residential data to more accurately assess the exposure as well as to determine the variability and uncertainty of the data. As a result, major changes were made in this section and the exposures were re-calculated to reflect current DPR regulations. Since no additional worker exposure data were available, the assessment of worker exposures continued to be based on point estimates. The variability and uncertainty in the data still could not be quantified. A distributional analysis of methyl bromide air concentration along the buffer zone perimeter was performed to assess residential exposure; however, it was limited to a single field application using both monitored data (Attachment H) and computer modeling (Johnson, 2001).

The NRC commented that the chronic exposure should include lifetime in the definition (NRC, 2000). DPR defines repeated exposures on an annual basis as chronic exposure. It does not account for the number of years of potential exposure in a lifetime because it is unknown how many years a worker or resident may be exposed to the pesticide of concern.

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[7] DPR field regulations include general requirements (tarps, acre limit, etc.), notification, minimum buffers, application methods, work hour limits, reentry intervals, tarp repair and removal procedures. The field permit conditions include procedures, guidance, and specifics for determining buffer zones. Structural fumigation regulations include tarp requirements, buffer zones, aeration and tarp removal procedures. The permit conditions for commodity, greenhouse, and potting soil fumigations include buffer zones, application methods, and work hours limitations. This list is not intended to be all inclusive and the full text of the permit conditions and regulations should be consulted.

The toxicological endpoint for risk characterization is selected from repeated 1- or 2-year exposure studies. Lifetime exposure is considered when a pesticide of concern showed a potential to cause tumors. For lifetime exposure, the workers are assumed to work and be exposed for 40 years in a 75-year lifetime, and the residents are assumed to be exposed for the entire lifetime of 75 years.

IV.B.1. Occupational Exposures

The database used to determine occupational exposures was the same as that used in the draft RCD/1999. However, the worker exposure estimates were substantially revised after re-evaluation of the database, examination of the methodology to estimate the exposure, and incorporation of current DPR regulations (Tables 19 to 21 based on Appendix E of Attachment F). Some occupational exposure scenarios were eliminated because of various reasons including change in use practices (detailed discussion in Attachment F). Others were not included because of lack of data or the type exposure was not anticipated. For example, chronic exposure of workers associated with field fumigation was not considered because methyl bromide is used primarily during pre-planting. The exposures for tarp removers measured on the same day as tarp was cut as well as pipe laying activity during fumigation were eliminated because such practices were no longer in compliance with the DPR regulations.

In terms of the methodology to estimate the exposure levels, an upper bound value was used, instead of the only measured value or the highest value, to estimate the acute exposures of workers in field fumigations. This change was necessary to be consistent with the upper bound approach used to determine work hour restrictions in the DPR regulations (Gibbons and Thongsinthusak, 2000). The equation used to calculate the upper bound values was defined as:

upper bound = mean or only measured level + (1.645 x standard deviation)

It should be noted, the upper bound values for most work scenarios were based on a single or two measurements (n values indicated in Tables 19-21). In these cases, the standard deviation was assumed to be equal to that data point or the average of two data points. In almost all cases, the upper bound values were greater than the values in the draft RCD/1999.

In addition, the upper bound exposures were adjusted based on the work hours restrictions in the DPR regulations with the maximum daily exposure not to exceed 210 ppb. For example, the field fumigation applicator exposure was calculated based on the permitted work hour of 4 hours instead of the 5.8 hours determined from the surveys (see Attachment F). For commodity fumigation, the acute exposure for all workers was set at 210 ppb. The DPR regulations required monitoring of the work site and reduction of work hours accordingly to meet the 210 ppb daily limit. For durations longer than acute exposure, the exposures were either based on 210 ppb (n=0 in Tables 20 and 21) as the daily exposure or the average measured values when they do not exceeded 210 ppb. These exposures were then amortized by the number of days work within the specified period. The total duration for these periods were 7, 90, and 365 days for short-term, subchronic, and chronic exposures, respectively.

Structural Fumigation

The inhalation exposures of applicators in structural fumigation were not determined because they are required to wear self-contained breathing apparatus. No data were available for other workers such as tarp removers.

Field Fumigation

For pre-treatment of soil before planting, two groups of fumigation were assessed: shallow-shank injection with tarp and deep-shank injection without tarp. General duties of the workers were: (1) Applicator drives application rig with the cab which could be enclosed or equipped with an overhead fan, (2) Copilot assists the applicator. He may be on a raised platform, (3) Shovel-man turns the rig around at the end of a row and seals row ends, (4) Cultipacker driver- drives a cultipacker which compacts the soil after application, (5) Disc driver- drives a second tractor which a disc to compact the soil after application, (6) Tarp cutter or tractor driver drives a vehicle which cuts the tarp, and (7) Tarp remover (basket-man, end puller) removes and gathers the cut tarp from the field. For both groups of fumigation, the monitoring studies were conducted primarily to determine the effectiveness of modifications to existing application procedures and aeration of treated fields. As such, these studies generally contained only 1 to 2 samples. Collectively, they showed that some modifications were effective in reducing exposure and those modifications were subsequently included in the regulations for the use of methyl bromide in field fumigation.

With shallow-shank and tarp fumigation (Table 19a to f), workers involved in the application with no modifications (Table 19a) had higher exposures than those in other methods (Table 19b to d). The applicator, copilot, and shovel-man acute exposures were 188 ppb, 245 ppb, and 191 ppb, respectively, based on 8 to 10 measurements. With the addition of scrapers (closing shoes), rollers, and/or raised platforms (Table 19b to d), these devices appeared to lowered the exposures for these workers. The best method involved both swept-back shank and closing shoes (Table 19d) where the applicators, copilots, and shovel-men exposures were 4 ppb, 58 ppb, and 1 ppb, respectively. The driver (7 ppb) and copilot (62 ppb) of the tractor in the placement of tarp had lower acute exposures than those involved in the application. For tarp cutting and removal, one study showed acute exposures of 202 ppb (cutter, 3 samples) and 215 ppb (puller, 12 samples) (Table 19e). Another study showed cutters, tractor drivers, basket-men, and end pullers with higher acute exposures; they were 138 ppb, 1058 ppb, 1003 ppb, and 22 ppb, respectively (Table 19f). These were based on single measurements.

With deep-shank injection, the applicators with only overhead fan had the highest acute exposure at 281 ppb (Table 19g). Lower acute exposures were measured for applicators in tractors with modifications. These included overhead fan and scrapers and rollers (104 ppb, Table 19h), enclosed cab (161 ppb and 171 ppb, Table 19i), and enclosed cab with scrapers (13 ppb, Table 19j). When a second tractor with a disc or cultipacker was involved, the drivers had relatively lower exposure (13-181 ppb) than those for applicators, except for the disc driver (934 ppb Table 19i).

For both short-term and subchronic exposures in shallow-shank and deep-shank methods, the exposure patterns were similar to those for acute exposures which were the basis for the calculations. Chronic exposure was not expected for any of the work scenarios.

For workers at adjacent fields, there were no data for their exposures. Since the buffer zone for acute exposure is set at 210 ppb and they are only allowed to work outside of the buffer zone, their exposures could be assumed to be at or less than 210 ppb.

Commodity/Brewery Fumigation

For workers with potting soil in greenhouses, the maximum acute exposure was set at 210 ppb (Table 20a). Their actual exposures were relatively low because tarp venters are required to wear self-containing breathing apparatus and tarp removal occurs after 48 hours of venting. The short term exposures, based on measured values, were 0.001 ppb and 0.14 ppb for these two group of workers. No subchronic or chronic exposures were determined for this activity. No data were available for other workers, e.g., applicators, associated with this use.

The acute exposure of all workers in commodity fumigation facilities was also limited 210 ppb (Table 20b and c). The exposures for other exposure durations were based on the average of measured values. The workers included those who were directly involved with the fumigation (applicators, aerators, leak checkers), those who handled fumigated products (forklift drivers, sorters, packaging workers), and those who worked in the facilities doing other jobs.

For workers involved in the fumigation of grain products, the range of short-term exposures was 0.02 ppb (aerator of tarpaulin fumigation) to 11 ppb (forklift driver emptying sea containers/truck trailers) (Table 20b). These forklift drivers also had the highest exposure of 8 ppb for subchronic and chronic exposures. In comparison, forklift drivers emptying non-certifying fumigation chambers had much lower exposures (3 ppb) for these durations.

For workers involved in the fumigation of raisins, the range of short-term exposures was 3 ppb (Table 20c. forklift driver) to 180 ppb (Table 20c. worker involved in clear chamber for raisins). For workers in a walnut processing plant (Table 20c2), potential exposures were based on air sampling of work stations rather than specific tasks. Workers in clearing plant (178 ppb) and vacuum chamber (180 ppb) had the highest methyl bromide levels for short-term exposure compared to other areas. The lowest average short-term level (25 ppb) was measured in the special cracking area. For both raisin and walnut workers, the short-term and subchronic exposure levels were similar because the fraction of time worked (6 days per 7 days short-term, 63-75 days per 90 days seasonal) during those periods was almost the same. Chronic exposure was considered for raisin processing workers but was not expected for most of walnut processing workers.

For workers in a brewery, exposures were estimated for applicators and aerators at various locations (Table 20d). This type of fumigation is similar to structural fumigation and no other workers are allowed in the facility during fumigation. The exposure levels were slightly higher during aeration than fumigation. The short-term exposure level ranges were 7-49 ppb for aerators and 8-12 ppb for applicators. No seasonal or chronic exposures were expected.

For workers in the facilities but whose tasks were not directly related to commodity fumigation, data were available only for raisin and walnut fumigations. The exposure levels were either based on the acute level of 210 ppb or measured by ambient and area sampling (Table 21). The range of short-term exposures was 7 ppb (hopper area for raisins, Table 21a) to 180 ppb (walnut sorting and packaging areas, Table 21b2). The subchronic and chronic

exposures (except for walnut processing) were comparable to those for short-term levels because of the frequency of exposure. The estimated number of work days were 6 days per 7 day period, 63-75 days per 90 day period, and 150 per 365 day period, for short-term, subchronic, and chronic exposures, respectively.

IV.B.2. Residential Exposures

Structural Fumigation

The exposures of residents returning to homes after fumigation and aeration were not estimated due to lack of data on current practices. The durations of exposure expected are acute and short-term as methyl bromide off-gas from confined air space such as the wall space. DPR regulations limit the acute exposure at or less than 210 ppb by modification of application methods, aeration time (72 hours of active aeration or 7 days for nonmechanical or natural ventilation instead of the 24 hours used previously), and buffer zones around the fumigated homes (DPR, 2000b).

Field Fumigation

Residential exposures were determined along the buffer zone perimeter to determine the effectiveness of the buffer zone (Table 22a). Two types of distributional analyses were performed: the maximum concentration along the buffer zone perimeter, and the maximum distance required to keep the air concentration at or below the 210 ppb reference concentration for acute exposure (Johnson, 2001[8]). In these analyses, available field monitoring data (data summarized in Attachment H) were combined with computer modeling to generate the maximum air concentration or distance under a wide variety of conditions due to the field size, flux (emission rate), and meteorological conditions. The cumulative frequency distribution reflected the maximum concentrations or distances under the 24-hour meteorological data sets (7166 days from 20 years of data). It should be noted that the maximum concentration determined in these analyses occurred only on a portion of the buffer zone perimeter, and these analyses addressed only acute exposure. For longer durations, the exposures were not simulated at this time because of the complexity involved in determining the methyl bromide air levels from multiple field applications and different durations of exposure. Potential exposures from multiple uses are addressed in part by ambient air monitoring projects as described under All Uses and Table 22c.

The result of the maximum air concentration analysis was used in the exposure assessment to determine the acute residential exposure at the buffer zone perimeter after field fumigation. The data from Johnson (2001) were interpolated/extrapolated to derive emission rates representing the different fumigation methods (Attachment F). The emission rates (lbs mebr/acre-day) and the corresponding fumigation methods were: 80 (nontarp/ shallow/bed), 160 (tarp/deep/broadcast; nontarp/deep/broadcast), 200 (tarp/shallow/bed), 225 (drip system-

[8] The executive summary of the Johnson (2001) report is in Attachment H. The report contained additional analyses and responses to NRC questions on buffer zones. Only a limited amount of information of the report is contained in this document. The reader is referred to the complete report for details.

hot gas), and 320 (tarp/shallow/broadcast). The magnitude of the methyl bromide maximum air concentration was related to the size of the field and emission rate (depending on the method of application) (Table 22a). The maximum methyl bromide air concentrations from the 90th to the 99th percentiles (cumulative frequency of 0.9 to 0.99) were presented. For example, the maximum concentration along the buffer zone perimeter was 143 ppb for 1 acre fumigation and 80 lbs emission rate under 6449 (90% of 7166 input) different 24-hour meteorological data sets. At this same 90th percentile, the air concentrations were at or less than 210 ppb for other emission rates and acreage. At the 95th percentile, a level generally selected for risk characterization, the exposure ranges for each field sizes were: 161-174 ppb (1 acre), 163-215 ppb (10 acre), 201-225 ppb (20 acres), 213-230 ppb (30 acres), and 221-236 ppb (40 acres).

Commodity Fumigation

The acute exposure for residents living near commodity fumigation facilities was limited to 210 ppb (Table 22b). The exposures for the longer-term durations were based on the 210 ppb level and adjusted by the number of exposure days during the exposure period. They were broadly divided into two categories of low range (3/7 days, 30/90 days, and 150/365 days) and high (6/7 days, 75/90 days, and 185/365 days) range depending on the number of exposed days during the duration period. The exposures were 90-180 ppb (short-term), 70-175 ppb (subchronic), and 86-106 ppb (chronic).

All Uses

For residents living in methyl bromide use areas which may include field, commodity, and structural fumigations, the exposures were based on ambient air monitoring by the Air Resources Board (7-8 weeks of monitoring) at Kern, Monterey and Santa Cruz counties (ARB, 2000 and 2001) (Table 22c). For each monitoring site, the 95th percentile of all daily (24-hour) monitoring was calculated using lognormal methods (Powell, 2001). The weekly exposure values indicated in the Table were the 95th percentile of all weekly means using normal methods for each site. The 7-8 week exposure values were the arithmetic means of the weekly means. The data showed that the magnitude of the detected levels corresponded to the use (field and commodity fumigations) during the monitored period (DPR, 2001d). The 95th percentile daily exposure levels ranged from 0.239 ppb (Mettler Fire Station) to 30.2 ppb (Pajaro Middle School in Watsonville) (Table 22c). Levels at these two sites also provided the ranges for weekly (0.163 to 17.1 ppb), and 7-8 week (0.084 to 7.68 ppb) exposure durations. While there may be a potential for longer duration of exposure, a quantitative determination of the exposure cannot be made at this time (Attachment F). Since these studies showed some sites with methyl bromide levels 2- to almost 8-folds higher than the 7-week reference concentrations of 1 to 2 ppb (Table 18), additional monitoring has been conducted by the Air Resources Board (DPR, 2001b). DPR has also required the registrants to conduct ambient air quality monitoring in 2001-2002 (DPR, 2001c).

Table 19. Estimates of occupational exposures to methyl bromide in field fumigation.[a]

Type of Application	n[b]	Acute	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
a. Shallow-shank/ tarp / broadcast - (Noble plow, 10-12" injection, open cab and overhead fan for applicators; *Table B1,2,3*)					
Applicator	8	188	66	34	n/a
Copilot	7	245	99	51	n/a
Shovel-man	10	191	33	n/a	n/a
b. Shallow shank/ tarp/ bed - Scrapers (6-8" injection, conventional shank, copilot on raised platform in one case, scrapers/closing shoes and rollers to compress the soil after injection in the other case; *Table B9*)					
1. Raised platform					
Applicator	1	146	47	25	n/a
Copilot	2	190	61	32	n/a
2. Closing shoes					
Applicator	1	80	26	13	n/a
Copilot	2	305	99	51	n/a
c. Shallow shank/ tarp/ bed - Drip tape (12-14" injection; swept-back shank, first tractor forms bed, injects methyl bromide, and puts on drip tape; second tractor lays on tarp; *Table B10*)					
1. Tractor fumigation					
Driver	1	51	17	9	n/a
Applicator	1	82	27	14	n/a
Drip tape layer	1	119	19	n/a	n/a
2. Tractor with tarp					
Driver	1	7	2	1	n/a
Copilot	2	62	20	10	n/a
d. Shallow shank/ tarp/ bed - Closing device (6-8" injection, swept-back shank, use of a closing device and compaction roller to compress the soil before tarp application; *Table B11*)					
Applicator	1	4	1	1	n/a
Copilot	2	58	19	10	n/a
Shovel-man	2	1	0.2	n/a	n/a
e. Shallow shank/ tarp - Tarp removal study 1 (10-12" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; *Table B12*)					
Cutter	3	202	39	18	n/a
Puller	12	215	28	13	n/a
f. Shallow shank/ tarp - Tarp removal study 2 (10" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; *Table B13*)					
Cutter	1	138	37	17	n/a
Remover:tractor driver	1	1058	286	133	n/a
Remover:basket-man	1	1003	271	126	n/a
Remover:end puller	1	22	6	3	n/a

Table 19. Estimates of occupational exposures to methyl bromide in field fumigation (continued).[a]

Type of Application	n[b]	Acute	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
g. Deep-shank/ non-tarp - Overhead fan (20-24" injection, open cab and overhead fan for applicators; *Table B6*)					
Applicators	2	281	91	47	n/a
Copilot	1	89	29	15	n/a
Cultipacker	1	181	59	n/a	n/a
h. Deep-shank/ non-tarp - Overhead fan and scrapers (20-24" injection, open cab and overhead fan for applicators, scrapers and press wheels to compress the soil after injection; *Table B6*)					
Applicator	1	104	34	17	n/a
Cultipacker	1	128	41	n/a	n/a
i. Deep-shank/ non-tarp - Enclosed cab (24" injection, enclosed cab for applicators, closing scrapers, second tractor equipped with either a disc or cultipacker; *Table B7*)					
1. Disc					
Applicator	1	161	52	27	n/a
Disc driver	1	934	303	157	n/a
2. Cultipacker					
Applicator	2	171	56	29	n/a
Supervisor	1	122	40	21	n/a
Cultipacker	2	62	20	n/a	n/a
j. Deep-shank/ non-tarp - Enclosed cab and scrapers (27" injection, enclosed cab for applicators, scrapers and rollers to compress the soil after injection; *Table B8*)					
Applicator	1	13	4	2	n/a
Cultipacker	1	13	4	n/a	n/a

a/ Detailed description of the exposure scenarios are provided in Attachment F and values from Appendix E. with Table number indicated in italics for cross reference. n/a= not applicable or no exposure data available. General duties of the workers: Applicator- drives application rig and inside the cab with or with enclosure or overhead fan. Copilot- assists the applicator. He may be on a raised platform as in f. Shovel-man- turns rig around at the end of a row and seals row ends. Cultipacker driver- drives a cultipacker which compacts the soil after application. Disc driver- drives a second tractor which a disc to compact the soil after application. Tarp cutter- drives a tractor which cuts the tarp. Tarp remover- removes the tarp from the field (tractor driver, basket-man, end puller).

b/ n=number of measurements. These measured value(s) were used to determine the upper bound value for acute exposure. The average of measured values was amortized for other exposure durations.

Table 20. Estimates of occupational exposures to methyl bromide in commodity fumigation.[a]

Type of Application	n[b]	Acute[c]	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean(ppb)
a. Greenhouse potting soil-hot gas method					
Tarp venter	4	210	0.001	n/a	n/a
Tarp remover	4	210	0.14	n/a	n/a
b. Fumigation of grain products					
Aerator (container/trailer)	3	210	0.43	0.3	0.3
Aerator (tarp)	3	210	0.02	0.01	0.01
Forklift driver (container)	3	210	11	8	8
Forklift driver (chamber)	3	210	4	3	3
c. Fumigation of dried fruit and tree nut products					
1. Raisins					
Fumigator	2	210	54	44	26
Aerator	2	210	40	33	19
Clear chamber	0	210	180	147	86
Stem picker	2	210	24	20	12
Forklift driver	1	210	3	2	1
Hopper operator	1	210	16	13	8
2. Walnut processing					
Bulk packaging	2	210	29	28	n/a
Cleaning plant	12	210	178	173	n/a
Fumigatorium	3	210	75	73	43
Packaging	1	210	38	37	n/a
Vacuum chamber	0	210	180	175	n/a
Sorting	6	210	27	27	n/a
Special cracking	4	210	25	24	n/a
d. Fumigation and aeration at a brewery facility					
1. Applicator					
Entry to open canister	4	210	8	n/a	n/a
Area sample	1	210	12	n/a	n/a
2. Aerator					
Aerator	2	210	7	n/a	n/a
Area sample (entrance)	1	210	49	n/a	n/a
Area sample (truck)	1	210	29	n/a	n/a

a/ Data from Attachment F. n/a= not applicable or no exposure data available.
b/ n=number of measurements. The average measured value(s), if they do not exceed 210 ppb, were used to determine the exposures for durations longer than that for acute. For n=0, 210 ppb was used as the average value.
c/ The worker exposure was set at 210 ppb, the maximum limit in the DPR regulations.

Table 21. Ambient and area air sampling of methyl bromide in commodity fumigation facilities.[a]

Type of Application	n[b]	Acute[c]	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
a. Chambers (raisins)					
Chamber	1	210	75	62	36
Cage	1	210	46	38	22
Leak checker	2	210	n/a	n/a	n/a
Aeration	2	210	99	81	48
Clearing	2	210	39	32	19
Hopper area	2	210	7	6	3
Stem picker area	4	210	23	19	11
b. Walnut processing facility					
1. Area samples					
Sorting line	2	210	24	n/a	n/a
2. Compliance monitoring					
Sorting line	0	210	180	175	n/a
Cello packaging	0	210	180	175	n/a
Bulk packaging	0	210	180	175	n/a

a/ Detailed description of the exposure scenarios are provided in Attachment F. n/a= not applicable or no exposure data available.

b/ n=number of measurements. The average measured value(s), if they do not exceed 210 ppb, were used to determine the exposures for durations longer than that for acute. For n=0, 210 ppb was used as the average value.

c/ The worker exposure was set at 210 ppb, the maximum limit in the DPR regulations.

Table 22. Residential exposures to methyl bromide from living near field or commodity fumigation activities.

a. At buffer zone perimeter of fumigated fields- Acute exposure[a]						
Field size	Cumulative frequency	Methyl bromide concentration (pbb) for different emission rates (80-320 lbs methyl bromide /acre-day)				
		80	160	200	225	320
1 acre	0.9 **0.95** 0.97 0.99	143 ppb **161** 175 211	152 ppb **174** 191 239	151 ppb **174** 191 241	150 ppb **174** 192 241	148 **173** 195 243
10 acres	0.9 **0.95** 0.97 0.99	190 **215** 236 290	175 **203** 224 283	170 **198** 219 276	163 **190** 212 268	138 **163** 186 236
20 acres	0.9 **0.95** 0.97 0.99	198 **225** 248 304	183 **212** 234 297	178 **207** 230 290	176 **206** 229 289	171 **201** 225 286
30 acres	0.9 **0.95** 0.97 0.99	204 **230** 255 312	183 **213** 235 298	183 **213** 236 299	183 **214** 238 301	186 **218** 242 309
40 acres	0.9 **0.95** 0.97 0.99	210 **236** 263 321	190 **222** 246 312	189 **221** 245 310	190 **223** 247 313	196 **229** 255 324

b. Near commodity fumigation facilities[b]				
Type of Application	Acute	Short-term	Sub-chronic	Chronic
	upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
low range	210	90	70	86
high range	210	180	175	106

Table 22. Residential exposures to methyl bromide from living near field or commodity fumigation activities (continued).

c. Ambient monitoring in three California counties[c]				
Sites in California	Daily (ppb)	Weekly (ppb)	7-8 weeks (ppb)	Chronic
Monterey				
Chualar School, Chualar	**2.26**	1.63	0.644	No data
La Joya Elementary School, Salinas	**18.5**	11.1	3.79	
Oak Avenue School, Greenfield	**1.21**	0.918	0.387	
Pajaro Middle School, Watsonville	**30.2**	17.1	7.68	
Ambient Monitoring Station, Salinas	**6.17**	3.14	1.29	
Santa Cruz				
Salsepuedes Elementary School, Watsonville	**12.2**	7.45	2.6	
Kern				
Ambient Monitoring Station, Bakersfield	**0.556**	0.507	0.189	
Cotton Research Station, Shafter	**25.4**	5.54	2.16	
Mettler-Fire Station, Mettler	**0.239**	0.163	0.084	
Mountain View School, Lamont	**0.262**	0.195	0.092	
Shafter-Walker Ambient Monitoring Station	**3.98**	2.05	0.792	
Vineland School District, Bakersfield	**0.292**	0.181	0.099	

a/ Based on air concentrations in Johnson, 2001. The emission rates (lbs mebr/acre-day) and the fumigation methods are in Attachment F and are: 80 (nontarp/shallow/bed), 160 (tarp/deep /broadcast; nontarp/deep/broadcast), 200 (tarp/shallow/bed), 225 (drip system-hot gas), and 320 (tarp/shallow/broadcast). The concentrations in ug/m^3 was converted to ppb using a factor of 3.89. Bolded values are at the 95th percentile.

b/ Low range= 3 days/7 days, 30 days/90 days, and 150 days/365 days for short-term, subchronic, and chronic exposure, respectively, as described in Attachment F. High range= 6 days/7 days, 75 days/90 days, and 185 days/365 days for short-term, subchronic, and chronic exposure, respectively.

c/ Data from Attachment F. Air monitoring was done for 7-8 weeks. Daily=95th percentile of all measured values, weekly=mean values, 7-8 weeks= means of weekly means.

Table 23. Summary of occupational and residential exposures to methyl bromide.[a]

Scenarios	Workers at specific tasks (ppb)[b]				Workers around the use of methyl bromide (ppb)[c]				Residential exposures (ppb)[d]			
	acute	short-tem	sub-chronic	chronic	acute	short-term	sub-chronic	chronic	acute	short-term	sub-chronic	chronic
Structural Fumigation												
Houses	No exposure since SCBA is required. No data on tarp removers				NA				assume 210 ppb	No data		
Field Fumigation												
Shallow-shank Deep-shank	1-1058 13-934	1-286 4-303	0.2-133 2-157	NA NA	assume 210 ppb	No data		NA	161-236 at 95th %	No data		
Commodity Fumigation												
Green-house soil	210*	0.001-0.14	NA	NA	No data				210*	90*-180*	70*-175*	86*-106*
Grains	210*	0.02-11	0.01-8	0.01-8	No data							
Raisins	210*	3-180*	2-147*	1-86*	210*	7-99	6-81	3-48				
Walnut	210*	25-180*	24-175*	43	210*	24-180*	175*	NA				
Brewery	210*	8-49	NA	NA	NA							
Other uses	No data				No data							
All Uses												
Ambient air	NA								0.239-30.2	0.163-17.1	0.084-7.68	No data

a/ Data were presented in Tables 19-22. NA=not applicable as exposure was not expected. * =exposure was based on 210 ppb as the acute exposure or the daily exposure value for amortization to calculate other durations of exposure.
b/ Table 19 for field fumigations and Table 20 for commodity fumigation.
c/ Table 21 for commodity fumigation.
d/ Table 22a for field fumigations, 22b for commodity fumigation, and 22c for ambient air monitoring.

IV.C. RISK CHARACTERIZATION

The potential health hazard associated with the use of methyl bromide was considered for occupational and residential exposures. Non-oncogenic effects were characterized in terms of a margin of exposure (MOE), defined as the ratio of the critical human equivalent NOEL to the estimated human exposure levels. The oncogenic risk of exposure to methyl bromide was not evaluated since methyl bromide has not been shown to be oncogenic based on the current database. The human equivalent NOELs are listed in Table 18 and the exposure levels for the various exposure scenarios are presented in Tables 19 to 22 and summarized in Table 23. The calculated MOEs are shown in Tables 24 to 27 and a summary is presented in Table 28.

IV.C.1. Occupational Exposure

Structural Fumigation

Margins of exposures were not calculated for workers involved in structural fumigation. The acute MOE for the applicators was assumed to be greater than 100 since these workers are required to be in a self-contained breathing apparatus.

Field Fumigation

With shallow-shank/tarp/broadcast fumigation (Table 24a to f), the acute MOEs were 112 (applicator), 86 (copilot), and 110 (shovel-man) for workers Noble plow and overhead fan (Table 24a). The MOEs were higher for the workers in shallow-shank/tarp/bed fumigation and various equipment modifications. The MOEs for these applicators were 144 and 263 (Table 24b, conventional shank and scrapers), 256 (Table 24c with swept-back shank), and 5250 (Table 24d swept-back shank and closing device). For copilots, the MOEs varied depending on the modification. The MOE was 69 when a conventional shank was used, even though scrapes/closing shoes were added. The MOEs were 111 when the copilot was in a raised platform (Table 24b) and 362 when swept-back shank and closing device were used in the application (Table 24d). The MOEs for the driver and copilot in the second tractor for tarping were 3000 and 339, respectively. The MOEs for workers in tarp cutting and removal varied depending on the study even though similar procedures were used. However, there were more measurements in the first study (3 to 12 samples) compared to the second study (1 sample each). In study 1 (Table 24e), the MOEs were 104 and 98 for cutters and pullers. In the second study (Table 24f), the MOEs were 152 (cutter), 20 (remover:tractor driver), 21 (remover:basket-man), and 955 (remover:end puller).

With deep-shank injection, the applicators with only overhead fan had the lowest MOE of 75 (Table 24g). The MOEs were higher with modifications and were: 202 (Table 24h, open cab with scrapers), 130 and 123 (Table 24i, enclosed cab), and 1614 (Table 24j, enclosed cab and scrapers/rollers). The MOEs for driver in the second tractor with a cultipacker were also higher when scrapers were used after application. The MOE increased from 116 (no modifications, Table 24g) to 164-1615 (use of scrapers and/or rollers, Table 24h-j). The MOE was only 22 for the disc driver (Table 24i1).

For both shallow-shank and deep-shank methods, the MOEs for almost all short-term exposures were 100 while subchronic exposures were less than 100. Chronic exposure was not expected for any of the work scenarios.

For workers at adjacent fields, the acute MOE could be assumed to be 100 with the exposure not to exceed 210 ppb.

Commodity/Brewery Fumigation

The acute MOEs for all workers in commodity fumigation facility were 100 because their upper exposure limit was 210 ppb (Tables 25 and 26). For tarp ventors and removers of potting soil fumigation in greenhouses, the MOEs for short-term exposures were greater than 80,000 because of their relatively low actual exposures (Table 25a). No data were available for other workers.

In the fumigation of grain products, MOEs for these workers were greater than 100 for the aerators for all exposure periods (Table 25b). For forklift drivers, the short-term MOEs were > 1000 but the subchronic and chronic MOEs were less than 100 (MOEs of 25 and 67). For workers involved in the fumigation of raisins, the range of MOEs for short-term exposures was 4000 (Table 25c1. forklift driver) to 67 (Table 25c1. worker involved in clear chamber for raisins). The MOE of 67 was based on the use of 210 ppb as the daily exposure value. The MOEs for subchronic and chronic exposures were less than 100, except for the forklift drivers with a MOE of 100. For workers in a walnut processing plant, the MOE was 67 for workers with the highest exposures (in clearing plant or vacuum chamber, Table 25c2). This MOE was based on measured values (cleaning plant) and the 210 ppb limit (vacuum chamber). The highest MOE was 480 for workers at the special cracking area. The MOEs for subchronic and chronic exposures were less than 10. For workers in a brewery, the MOEs for applicators and aerators were ranged from 245 to 1714 (Table 25d).

For workers in fumigation facilities not directly related to fumigation, the short-term exposure MOEs were generally greater than 100 (MOE of 121 to 1714) for raisin facilities. The short-term MOE for walnut processing was 500 based on area sampling but was 67 based on 210 ppb as the daily exposure level in sorting and packaging areas (Table 26b.2). However, the subchronic and chronic exposure MOEs for both raisins and walnut processing facilities were less than 100 based on either measured values or 210 ppb.

IV.C.2. Residential Exposure

Structural Fumigation

For residents living in treated home after aeration, the acute MOEs were not calculated due to lack of exposure data. They were expected to be at least 100 since regulations were based on the 210 ppb for acute exposure.

Field Fumigation

For the 95th percentile exposure at the buffer zone perimeter, the acute MOE ranged from 89 (40 acres/80 lbs) to 131 (10 acres/80 lbs) (Table 27a). The interpretation of these MOEs is not as straight forward as those based on point estimates since they are based on a frequency distribution and on maximum air concentrations along the perimeter. When the MOE is less than 100 based on a 95th percentile value, it means that the reference concentration of 210 ppb was exceeded in less than 5% of the 7166 24-hour meteorological data sets and only along the portion of the buffer zone perimeter with the maximum methyl bromide air

concentration. At the 90th percentile methyl bromide air concentration, all MOEs were at or greater than 100. At the 95th percentile, the MOEs were at least 100 (98 to 131) for 1 and 10 acres and all emission rates. For 20 and 30 acres, the MOEs were around 100 (96 to 104) with the exception of 91 and 93 for 80 lbs emission rate. For 40 acres, the MOEs were 89 to 95 for the specified emission rates.

Commodity Fumigation

The acute MOE for residents living near commodity fumigation facilities was 100 because the exposure was assumed to be 210 ppb (Table 27b). However, the MOEs were 39-78, 1, and 1, respectively, for short-term, subchronic, and chronic exposures based on 210 ppb as the average daily exposure levels.

All Uses

For residents living around methyl bromide uses, ambient air monitoring of 12 sites showed MOEs ranged from 695 to >80,000 for acute exposure, and from 409 to > 40,000 for short-term exposures (Table 27c). For 7-8 weeks of exposure, the MOEs for 7 of the sites were greater than 100 (range form 126 to 1190). The MOEs for the remaining sites ranged from 13 (Pajaro Middle School) to 78 (Salinas Ambient Monitoring Station).

Table 24. Margins of exposure for occupational exposures to methyl bromide in field fumigations.[a]

Type of Application	n[b]	Acute	Short-term	Subchronic	Chronic
a. Shallow-shank/ tarp / broadcast - (Noble plow, 10-12" injection, open cab and overhead fan for applicators; *Table B1,2,3*)					
Applicator	8	112	182	6	n/a
Copilot	7	86	121	4	n/a
Shovel-man	10	110	364	n/a	n/a
b. Shallow shank/ tarp/ bed - Scrapers (6-8" injection, conventional shank, copilot on raised platform in one case, scrapers/closing shoes and rollers to compress the soil after injection in the other case; *Table B9*)					
1. Raised platform					
Applicator	1	144	255	8	n/a
Copilot	2	111	197	6	n/a
2. Closing shoes					
Applicator	1	263	462	15	n/a
Copilot	2	69	121	4	n/a
c. Shallow shank/ tarp/ bed - Drip tape (12-14" injection; swept-back shank, first tractor forms bed, injects methyl bromide, and puts on drip tape; second tractor lays on tarp; *Table B10*)					
1. Tractor fumigation					
Driver	1	412	706	22	n/a
Applicator	1	256	444	14	n/a
Drip tape layer	1	176	632	n/a	n/a
2. Tractor with tarp					
Driver	1	3000	6000	200	n/a
Copilot	2	339	600	20	n/a
d. Shallow shank/ tarp/ bed - Closing device (6-8" injection, swept-back shank, use of a closing device and compaction roller to compress the soil before tarp application; *Table B11*)					
Applicator	1	5250	12000	200	n/a
Copilot	2	362	622	20	n/a
Shovel-man	2	21000	60000	n/a	n/a
e. Shallow shank/ tarp - Tarp removal study 1 (10-12" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; *Table B12*)					
Cutter	3	104	308	11	n/a
Puller	12	98	429	15	n/a
f. Shallow shank/ tarp - Tarp removal study 2 (10" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; *Table B13*)					
Cutter	1	152	324	12	n/a
Remover:tractor driver	1	20	42	2	n/a
Remover:basket-man	1	21	44	2	n/a
Remover:end puller	1	955	2000	67	n/a

Table 24. Margins of exposure for occupational exposures to methyl bromide in field fumigation (continued).[a]

Type of Application	n[b]	Acute	Short-term	Subchronic	Chronic
g. Deep-shank/ non-tarp - Overhead fan (20-24" injection, open cab and overhead fan for applicators; *Table B6*)					
Applicators	2	75	132	4	n/a
Copilot	1	236	414	13	n/a
Cultipacker	1	116	203	n/a	n/a
h. Deep-shank/ non-tarp - Overhead fan and scrapers (20-24" injection, open cab and overhead fan for applicators, scrapers and press wheels to compress the soil after injection; *Table B6*)					
Applicator	1	202	353	12	n/a
Cultipacker	1	164	293	n/a	n/a
i. Deep-shank/ non-tarp - Enclosed cab (24" injection, enclosed cab for applicators, closing scrapers, second tractor equipped with either a disc or cultipacker; *Table B7*)					
1. Disc					
Applicator	1	130	231	7	n/a
Disc driver	1	22	40	1	n/a
2. Cultipacker					
Applicator	2	123	214	7	n/a
Supervisor	1	172	300	10	n/a
Cultipacker	2	339	600	n/a	n/a
j. Deep-shank/ non-tarp - Enclosed cab and scrapers (27" injection, enclosed cab for applicators, scrapers and rollers to compress the soil after injection; *Table B8*)					
Applicator	1	1615	3000	100	n/a
Cultipacker	1	1615	3000	n/a	n/a

a/ Margins of exposure were based on exposure levels in Table 19 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term, 20 ppm (adult equivalent of 12 ppm) for neurotoxicity in rabbits; subchronic, 0.5 ppm (adult equivalent of 200 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (adult equivalent of 200 ppb) for nasal epithelial hyperplasia/degeneration in rats.

b/ n=number of measurements.

Table 25. Margins of exposure for occupational exposures to methyl bromide in commodity fumigation.[a]

Type of Application	n[b]	Acute	Short-term	Subchronic	Chronic
a. Greenhouse potting soil- hot gas method					
Tarp ventor	4	100	>100000	n/a	n/a
Tarp remover	4	100	85714	n/a	n/a
b. Fumigation of grain products					
Aerator (sea container/trailer)	3	100	27907	667	667
Aerator (tarp)	3	100	>100000	20000	20000
Forklift driver (container/trailer)	3	100	1091	25	25
Forklift driver (chamber)	3	100	3000	67	67
c. Fumigation of dried fruit and tree nut products					
1. Raisins					
Fumigator	2	100	222	5	8
Aerator	2	100	300	6	11
Clear chamber	0	100	67	1	2
Stem picker	2	100	500	10	17
Forklift driver	1	100	4000	100	200
Hopper operator	1	100	750	15	25
2. Walnut processing facility					
Bulk packaging	2	100	414	7	n/a
Cleaning plant	12	100	67	1	n/a
Fumigatorium	3	100	160	3	5
Packaging	1	100	316	5	n/a
Vacuum chamber	0	100	67	1	n/a
Sorting	6	100	444	7	n/a
Special cracking	4	100	480	8	n/a
d. Fumigation and aeration at a brewery facility					
1. Applicator					
Entry to open canisters	4	100	1500	n/a	n/a
Area sample	1	100	1000	n/a	n/a
2. Aerator					
Aerator	2	100	1714	n/a	n/a
Area sample	2	100	245-414	n/a	n/a

a/ Margins of exposure were based on exposure levels in Table 20 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term, 20 ppm (adult equivalent of 12 ppm) for neurotoxicity in rabbits; subchronic, 0.5 ppm (adult equivalent of 200 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (adult equivalent of 200 ppb) for nasal epithelial hyperplasia/degeneration in rats.

b/ n=number of measurements.

Table 26. Margins of exposure for occupational exposures to ambient and area air sampling of methyl bromide in commodity fumigation facilities.[a]

Type of Application	n[b]	Acute	Short-term	Subchronic	Chronic
a. Chambers (raisins)					
Chamber	1	100	160	3	6
Cage	1	100	261	5	9
Leak checker	2	100	n/a	n/a	n/a
Aeration	2	100	121	2	4
Clearing	2	100	308	6	11
Hopper area	2	100	1714	33	67
Stem picker area	4	100	522	11	18
b. Walnut processing facility					
1. Area samples					
Sorting line	2	100	500	n/a	n/a
2. Compliance monitoring					
Sorting line	0	100	67	1	n/a
Cello packaging	0	100	67	1	n/a
Bulk packaging	0	100	67	1	n/a

a/ Margins of exposure were based on exposure levels in Table 21 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term, 20 ppm (adult equivalent of 12 ppm) for neurotoxicity in rabbits; subchronic, 0.5 ppm (adult equivalent of 200 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (adult equivalent of 200 ppb) for nasal epithelial hyperplasia/degeneration in rats.

b/ n=number of measurements**.**

Table 27. Margins of exposure for residential exposures to methyl bromide from living near field or commodity fumigation activities.[a]

a. At buffer zone perimeter of fumigated fields- Acute exposure						
Field size	Cumulative frequency	Margins of exposure for different emission rates (80-320 lbs methyl bromide /acre-day)				
		80	160	200	225	320
1 acre	0.9 **0.95**	146 **131**	138 **121**	139 **121**	140 **121**	142 **122**
10 acres	0.9 **0.95**	111 **98**	120 **103**	124 **106**	129 **110**	152 **129**
20 acres	0.9 **0.95**	106 **93**	115 **99**	118 **101**	119 **102**	122 **104**
30 acres	0.9 **0.95**	103 **91**	115 **99**	115 **98**	115 **98**	113 **96**
40 acres	0.9 **0.95**	100 **89**	110 **95**	111 **95**	110 **94**	107 **92**

b. Near commodity fumigation facilities				
Type of Application	Acute	Short-term	Sub-chronic	Chronic
	upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
low range	100	78	1	1
high range	100	39	1	1

Table 27. Margins of exposure for residential exposures to methyl bromide from living near chamber or field fumigation activities (continued).[a]

c. Ambient monitoring in three California counties				
Sites in California	Daily (ppb)	Weekly (ppb)	7-8 weeks (ppb)	Chronic
Monterey				
Chualar School, Chualar	9292	4294	155	n/a
La Joya Elementary School, Salinas	1135	631	26	
Oak Avenue School, Greenfield	17355	7625	258	
Pajaro Middle School, Watsonville	695	409	13	
Ambient Monitoring Station, Salinas	3404	2229	78	
Santa Cruz				
Salsepuedes Elementary School, Watsonville	1721	940	38	
Kern				
Ambient Monitoring Station, Bakersfield	37770	13807	529	
Cotton Research Station, Shafter	827	1264	46	
Mettler-Fire Station, Mettler	87866	42945	1190	
Mountain View School, Lamont	80153	35897	1087	
Shafter-Walker Ambient Monitoring Station	5276	3415	126	
Vineland School District, Bakersfield	71918	38674	1010	

a/ Margins of exposure were based on exposure levels in Table 22 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term and weekly, 20 ppm (child equivalent of 7 ppm) for neurotoxicity in rabbits; subchronic and 7-8 weeks, 0.5 ppm (child equivalent of 100 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (child equivalent of 100 ppb) for nasal epithelial hyperplasia/degeneration in rats.

Table 28. Summary of margins of exposure for occupational and residential exposures to methyl bromide.[a]

Scenarios	Workers at specific tasks (ppb)[b]				Workers around the use of methyl bromide (ppb)[c]				Residential exposures (ppb)[d]			
	acute	short-tem	sub-chronic	chronic	acute	short-term	sub-chronic	chronic	acute	short-term	sub-chronic	chronic
Structural Fumigation												
Houses	Assume > 100 for applicators since SCBA is required. No data on tarp removers				No data				assume 100*	No data		
Field Fumigation												
Shallow-shank Deep-shank	20->1000 22->1000	42->1000 40->1000	2-200 1-100	n/a n/a	assume 100*	No data		NA	89-131 at 95th%	No data		
Commodity Fumigation												
Green-house soil	100*	>1000	NA	NA	No data				100*	39*-78*	1*	1*
Grains	100*	>1000	25->1000	25->1000	No data							
Raisins	100*	67*->1000	1*-100	2*-200	100*	121->1000	2-33	4-67				
Walnut	100*	67*-480	1*-8	5	100*	67*-500	1*	NA				
Brewery	100*	245->1000	NA	NA	NA							
Other Uses	No data				No data							
All Uses												
Ambient air	NA								695->1000	409->1000	13->1000	No data

a/ Data were presented in Tables 24 to 27. n/a=not applicable or exposure data were not available. “>1000" was used as the upper limit for this Table, actual MOEs are indicated in Tables 24 to 27. *= MOE was based on 210 ppb for acute exposure or average daily exposure.

b/ Table 24 for field fumigation and Table 25 for commodity fumigation.

c/ Table 26 for commodity fumigation.

d/ Table 27a for field fumigation, 27b for commodity fumigation, and 27c for ambient air monitoring levels.

V. RISK APPRAISAL FOR INHALATION EXPOSURE

V.A. INTRODUCTION

The human health risk assessment of methyl bromide was conducted for occupational and residential exposures. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects of a substance will occur in humans under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment of methyl bromide are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The uncertainties associated with the selection of the endpoints and the NOELs have already been discussed in some details (**IV.A. HAZARD IDENTIFICATION**).

V.B.1. Acute Toxicity

For acute inhalation exposure to methyl bromide, one of the critical NOELs was based on developmental effects observed in rabbits. The assumption was that methyl bromide will also cause developmental toxicity in humans. Epidemiological data were not available to support or refute this assumption for methyl bromide. Comparative studies of other agents showed that laboratory animal data were generally predictive of adverse developmental effects in humans (U.S. EPA, 1991). There are agents which caused developmental toxicity in laboratory animals but have not been clearly shown to be human developmental toxicants. Available human data were too limited to establish cause-effect relationships.

The risk for adults, based on developmental toxicity, may be overestimated because of the approach used to determine the human equivalent NOEL to calculate the margins of exposures. Consistent with the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), the developmental effects (gall bladder agenesis and fused sternebrae) observed at the end of the gestation (after 12 days of exposure) were assumed to be due a single day's exposure. The actual NOEL for a single day's exposure may be higher than that for 12-days of exposure. Furthermore, DPR determined a 24-hour time-weighed average dose by amortizing the NOEL from 6 hours to 24 hours of exposure using Haber's Rule (C^n x T=effect where n=1). This calculation resulted in an amortized dose that is one-fourth of the 6-hour NOEL and assumed that the dose would remain above the threshold for develop-mental effects. In an interim toxicology assessment for methyl bromide, the U.S. EPA also used amortization to determine the dose for the same endpoint. The calculated dosage (14 mg/kg/day) was different than the DPR dosage (21 mg/kg/day) because rabbit respiration rates used by DPR (0.54 m^3/kg/day) and U.S. EPA (0.37 m^3/kg/day) were different (Hansen, 1993;

Lewis, 1995). The NRC in the review of the draft RCD/1999 stated that the amortization method used by DPR was conservative since methyl bromide is likely to be less toxic at lower concentrations over a day (50 ppm for 24 hours) than a higher concentration within a shorter time period (6 hours at 200 ppm) (NRC, 2000). The DPR approach was considered to provide more protection for the residential exposures and not a factor for worker exposures.

On the other hand, a comparison of NOELs for neurotoxicity in the dog and human showed that the extrapolated level may not be an overestimation of the risk. As discussed in the Hazard Identification section (**IV.A. HAZARD IDENTIFICATION**), the human equivalent NOEL for neurotoxicity observed in the dog was 25 ppm for children. This level was comparable to the 21 ppm based on developmental toxicity in the rabbits. For comparison with neurotoxicity in humans, a report of worker exposure showed a LOEL of 35 ppm (Watrous, 1942) (**III.H.1. Occupational Exposure**). In that study, workers experienced anorexia, nausea, and headaches when exposed to an overall methyl bromide concentration of <35 ppm during a 2 week period (Watrous, 1942). If the actual no effect in one day is assumed to be 1/10 of the 35 ppm, then the NOEL would be 3.5 ppm. Using a default factor of 1/10 for intraspecies extrapolation, the regulatory level would be 0.35 ppm (or 350 ppb), a level only 1.5-fold higher than the 210 ppb (21 ppm x 1/10 for interspecies x 1/10 for intraspecies variations) for developmental toxicity used by DPR for regulation. However, there are uncertainities in determining whether the symptoms were associated with acute exposure in the Watrous (1942) study. First, the report did not specify whether the workers had previous exposures to methyl bromide. It is unlikely that inexperienced workers were used since all tasks were manually performed. Second, the report was not specific as to the relationship between actual exposure concentration and duration and symptoms observed. Higher exposures were likely to have occurred in the first week compared to the second week when control measures were instituted. It would have been useful to have individual data on the onset of symptoms as well as measured exposure concentrations for both weeks. Workers with both dermal and systemic effects due to methyl bromide spillage and other accidents, especially during the first week, were likely to be exposed to levels higher than 35 ppm.

Another comparison of the critical acute NOEL is with the OEHHA Hot Spots reference levels (OEHHA, 1999). The current DPR acceptable level for acute exposure is 0.21 ppm, as an average over 24 hours. The equivalent concentration for a one-hour period is 5 ppm. This level is higher than the 1 ppm, one-hour REL for mild effects issued by OEHHA. While the DPR level of 5 ppm may not appear to be protective of human health, there are several considerations that need to be taken into account. RELs are determined by OEHHA for airborne toxicants under the mandate of the Air Toxics “Hot Spots” Information and Assessment Act of 1987 (AB 2588). This program has different objectives and procedures than DPR. For example, OEHHA issues three different RELs, a level protective against mild adverse effects, a level protective against severe adverse effects, and a level protective against life-threatening effects. DPR regulates based on a single level. The basis of the OEHHA one-hour REL of 1 ppm also needs to be considered. The 1 ppm was determined from the Watrous study (1942). As discussed in the previous paragraph, there are several problems with this study. OEHHA assumed that the toxicity experienced by the workers was due to a single exposure to 35 ppm methyl bromide for two hours. It is the opinion of DPR that the systemic effects reported are likely due to cumulative toxicity of these workers with previous exposure to high levels of methyl bromide at the plant before and during the first week of the study. The actual one-hour peak exposure level for mild effects is likely to be higher than the REL of 1 ppm.

V.B.2. Subchronic Toxicity

The endpoints for the critical short-term and subchronic exposures were based on neurotoxicity in the pregnant rabbit (Sikov *et al.*, 1981) and dogs (Newton, 1994b), respectively. Since methyl bromide is a known neurotoxicant, these endpoints are appropriate to use for hazard identification and risk characterization. The severity of the effects (convulsion and paresis) observed in the pregnant rabbits at 70 ppm and death after treatment had stopped suggested that a margin of exposure greater than the conventional benchmark of 100 might have to be considered.

It has been suggested that the decreased responsiveness observed in the dog after 30 exposures to 5 ppm should not be considered a treatment-related effect and is thus not appropriate for use as the critical NOEL for subchronic exposure. This suggestion was based on the assumption that effects after repeated exposure were only related to total dosage. The calculated total dosage for "decreased responsiveness" was less than those for "decreased activity" which was considered a treatment-related effect. DPR considers the analysis an oversimplification of the biological processes involved in the manifestation of the observed effects since the mechanism is unknown. The most important consideration is that the decreased responsiveness was specifically reported by an animal neurologist who had examined all 48 dogs on test previously on two occasions.

V.B.3. Chronic Toxicity

There were uncertainties associated with the use of hyperplasia/degeneration to the nasal cavity as the endpoint to evaluate chronic inhalation toxicity. One uncertainty was the interspecies variability in the nasal cavity between rodents and humans. Compared to humans, the increased complexity of the nasal turbinates, the straighter nasopharyngeal region, and the lower regional flow rates of rats might alter the toxicity at given exposure concentrations (Schreider, 1986). Additional information on the deposition, reactivity, solubility, absorption, metabolism, and clearance of methyl bromide in the nasal cavity epithelium of animals and humans would permit additional consideration of interspecies dosimetric adjustment (Jarabek *et al.*, 1990; U.S. EPA, 1990). Such information would also help define the relative contributions of regional versus systemically absorbed methyl bromide in the etiology of nasal damage.

As already discussed in the **IV.A. HAZARD IDENTIFICATION 2.c. Chronic Toxicity-Inhalation**, the use of the chronic NOEL based on effects in the nasal cavity may underestimate the risk since this NOEL expressed as human equivalents (0.1 ppm) is the same as that for the NOEL based on neurotoxicity after subchronic exposure.

V.B.4. Extrapolation of Estimated No-Effect Level from the Lowest-Effect Level

In this RCD, both the subchronic and chronic NOELs were estimated from the LOEL, the lowest dose tested. It is the DPR policy to use the 10-fold uncertainty factor (UF) to estimate the NOEL from a LOEL. Therefore, the estimated subchronic NOEL was 0.5 ppm based on neurotoxicity observed in two of eight dogs exposed to 5 ppm for 34 exposures. For chronic exposures, the estimated NOEL was 0.3 ppm based on a LOEL of 3 ppm for nasal epithelial hyperplasia and degeneration in the rat.

Instead of using a default 10-fold UF, two approaches have generally been discussed. One approach is to use the NOEL/LOEL ratios from the database. The problem with this approach is that these ratios reflect largely the dose selection of the studies, instead of toxicity. Two examples are provided.

(1) Methyl bromide is lethal to all species and shows a steep dose-response relationship in most cases. In one study, all rats exposed to 220 ppm methyl bromide died (100% mortality) but none died at 100 ppm (Irish, 1940). This implied that the UF could be 2-fold. However, the data also showed that the rats at 100 ppm suffered severe neurotoxicity and some were moribund. Obviously, neither the dose with no mortality can be used as the NOEL for risk assessment, nor can the factor of 2 be used as the UF for this study or other studies.

(2) With the developmental toxicity study (Breslin *et al.*, 1990), the NOEL and LOEL were 40 ppm and 80 ppm, respectively, for increased incidences of gall bladder agenesis and other effects. This also implied a 2-fold UF for extrapolation. On the other hand, the NOEL and LOEL ratio was 10-fold for parental (decreased fertility) and progeny (decreased pup body weights) effects in the reproductive toxicity study (American Biogenics Corp., 1986).

A more appropriate approach is the consideration of the magnitude of the response at the LOEL (Dourson *et al.*, 1996). The 10-fold UF may be excessive if the response rate at the LOEL is marginal or low. On the other hand, the 10-fold UF may not be sufficient when the response at the LOEL is considered severe. If data are sufficient for determining the slope of the dose-response, a benchmark dose approach might be considered for estimating the NOEL.

In the case with the dog study used to derive the critical subchronic NOEL, there was a qualitative dose-response relationship between the exposure duration and concentration and the severity of neurotoxicity (Table 6). However, the magnitude of the response at the lowest dose (5 ppm) can not be compared with those at the higher doses since those experiments were not conducted for the same duration. Therefore, it is appropriate to use the 10-fold default factor as the UF for this study.

For the critical chronic NOEL, there was also a dose-response relationship between the exposure duration and concentration and the severity of the nasal cavity lesions in the rat (Table 8). At the LOEL (the lowest dose tested), the incidence was significantly elevated ($p \leq 0.05$), for both sexes, when compared to that in the controls. However, the lesion was described as very slight. The mildness of the lesion suggested that an UF of less than 10 might be sufficient to estimate the NOEL from the LOEL. While the default factor of 10-fold for the extrapolation was used as per DPR policy, a benchmark dose approach may be considered when guidelines for the use of the approach are established. The NRC in the review of the draft RCD/1999 concurred with the DPR discussion and suggested a factor of 3 (NRC, 2000). However, the NRC also pointed out that the current use of a factor of 10 and a different methodology resulted in reference concentrations (1 ppb and 2 ppb for children and adults, respectively) similar to that (1.3 ppb) determined by the U.S. EPA.

V.C. INHALATION EXPOSURE ASSESSMENT

As discussed in **IV.B. INHALATION EXPOSURE ASSESSMENT**, a limited number of exposure scenarios was assessed. Data were not available for many scenarios as some acute

exposures were assumed to be or limited to 210 ppb (Table 23). The 210 ppb limit was used for exposures of both workers (commodity fumigation) and residents (structural and commodity fumigations). Depending on the factors such as distance and frequency of fumigation, the use of 210 ppb as a default exposure might over- or underestimate the actual acute exposures. However, it could be an over-estimation of exposures for longer durations as it is unlikely that the limit of 210 ppb is reached everyday during the specified period.

Of the available data, there were many deficiencies in the overall database (except for residential exposure to field fumigation and ambient air monitoring). They included: (1) studies not in compliance with Good Laboratory Practices, in particular, absence of field fortification recovery studies; (2) some data are from interim, internal, or draft reports; (3) missing application rate and field fortification recovery information; and (4) lack of duration and frequency of exposure values for some work scenarios. Many exposure data were obtained from studies employing short monitoring periods and then amortized to the 24-hour time-weighed average. These amortized exposure data could overestimate or underestimate the actual exposures. Two potential areas of underestimation were the assumptions that (1) workers of specific work task will not have additional exposure from working in other work task(s) for the remainder of the workday, and (2) there was no overtime work during peak use season. The magnitude of these uncertainties can not be quantified at this time. One area of overestimation was the use of 50% recovery value to adjust all data. In some field studies, the adjustment resulted in more methyl bromide volatilized than was applied.

With respect to specific studies in field fumigation, one uncertainty in the exposure estimates was that they were largely based on studies conducted in an effort to devise equipment modifications to decrease exposure. As such, many of the studies had only one or two measurements. In Subdivision U, U.S. EPA required data for 3 locations and 5 replicates per location for each work task monitored (U.S. EPA, 1986c). But collectively, the data indicated that the modifications were effective in reducing worker exposures. Some of these exposures were further decreased by work hour restrictions in the DPR regulations. In addition, the assessment of acute exposure was based on “upper bound” values as defined in **IV.B.1. Occupational Exposures**. These upper bound values were not true statistical upper bounds because they were based on few measured values and the coefficient (1.645) in the equation was not adjusted for sample size. Nevertheless, these values were higher than the highest values obtained in each study for almost all cases. The use of the highest measured value is a general default approach for acute exposure when the database is limited. For workers involved in commodity fumigation, the sample size was also small (1 to 2 samples) for almost all cases. Since the acute exposure was limited to 210 ppb, the reference level, this sample size problem applied mainly to the short-term, subchronic, and chronic exposure durations. Exposure data from studies conducted in compliance with the DPR regulations are needed.

For residential exposure to field fumigation, there were also uncertainties in the determination of the maximum methyl bromide air concentration distribution along the buffer zone perimeter of fumigated fields (Johnson, 2001). Once applied, methyl bromide levels in the air depend on many factors including wind, air temperature, barometric pressure, and soil conditions. The simulated exposures considered only one variable that is currently amenable to quantification: meteorology. This variable was based on the weather conditions of areas (4 counties) of heaviest methyl bromide use. While the analyses used 7166 inputs representing varied conditions during the 20 years, they may still not accurately represent statewide

conditions. Regional differences in weather conditions may also produce different exposure estimates. However, it is not possible to do extensive monitoring in every region of California because DPR has limited resources, and methyl bromide is used under a wide variety of use, field, and weather conditions. Targeted ambient air monitoring high methyl bromide use areas and computer modeling remain the most cost-effective mean of determining exposure. Additional monitoring by the ARB and the registrant will be used to re-evaluate the exposure. The potential risk from repeated exposures was not addressed due to lack of data. While DPR has implemented regulatory controls to require time and distance separation between fumigations, monitoring data are needed to determine the effectiveness of these measures.

V.D. RISK CHARACTERIZATION

The MOEs for potential acute, subchronic, and chronic exposures were based on NOELs for toxicity observed in laboratory animals. When the NOEL for non-oncogenic effects is based on animal data, a MOE of 100 is generally considered adequate for protection against potential acute or chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability. These uncertainty factors assume that the average human is 10 times more sensitive to the effects of a chemical than the most sensitive laboratory animal, and that a sensitive individual is 10 times more susceptible than an average individual (Davidson *et al.*, 1986; Dourson and Stara, 1983).

V.D.1. Interspecies Extrapolation

The sensitivity of humans and laboratory animals to methyl bromide toxicity was difficult to compare because of inadequate exposure information in human case reports. For endpoints such as developmental toxicity and nasal hyperplasia/degeneration, there were no data for these effects in humans. For other endpoints such as death, human exposure levels were generally very high (> 1000 ppm) and the exposure durations were determined by the circumstance of cases and were limited to one individual in most cases. In addition, it is difficult to estimate the exposure since methyl bromide at high concentration tends not to be evenly distributed (Holling and Clarke, 1944). As a result, human case reports can not be used for comparison to the LC100 data from animal testing since the latter were experimentally determined and involved a large number of animals (Table 1). At lower concentrations of methyl bromide, a limited comparison was made with neurotoxicity observed in humans and dogs. In the following example, symptoms in humans appeared to be more severe than those in the dogs under similar exposure concentrations and durations (Table 29). However, a quantitative determination can not be made because of the scarcity of human data.

The current DPR default for interspecies extrapolation is a factor of 10-fold with respect to the dose. The NRC in the review of the draft RCD/1999 agreed with DPR on the use of the 10-fold interspecies uncertainty factor (NRC, 2000). Accordingly, methyl bromide air concentrations were converted to the “dose” by taking into account the exposure concentration and duration, as well as the intake rate (respiration rate) of the exposed population. This approach is similar to that generally used for dietary exposure studies. The no-effect level is expressed as the dose after taking into account the consumption rate, instead of the concentrations in the diet. Thus, the net interspecies adjustment included the interspecies ratio of the intake rate, duration, and the 10-fold uncertainty factor.

Table 29: Comparison of neurotoxicity in humans and dogs.

Dose and duration	Human	Dog
156 ppm for 5 hours		lacrimation (Newton, 1994a)
400 ppm for 24 hours	difficulty in breathing, headaches, nausea, skin rash (Reidy *et al.*, 1994)	
150 ppm for 8 hours	nausea, vomiting, dizziness; later seizures, headaches, nausea, ataxia, and others (Hustinx *et al.*, 1993)	
103 ppm for 9 days		↓activity and emesis (Newton,1994b)
53 ppm for 14 days		↓activity (Newton, 1994b)
overall <35 ppm over a 2 week period; onset and duration not specified	anorexia, nausea, headaches, vertigo, and other effects (Watrous, 1942)	

V.D.2. Intraspecies Extrapolation

For intraspecies variation in the response to methyl bromide, the default uncertainty factor of 10 was used because human illness/poisoning reports did not provide sufficient information to derive another factor. In these reports (discussed in **III.H. Neurotoxicity**), some individuals showed more severe symptoms than others. However, this difference in response was not quantified, and may only be quantified in well-conducted experimental studies. The NRC in the review of the draft RCD/1999 agreed with DPR on the use of the 10-fold intraspecies uncertainty factor (NRC, 2000).

Studies on the role of glutathione-S-transferase (GST) in methyl bromide metabolism and toxicity also provided evidence for variations in human response to methyl bromide. The glutathione-S-transferases are a multi-gene family of enzymes involved in the metabolism (activation and detoxification) of a wide variety of chemicals (Eaton and Bammler, 1999). They catalyze the general reaction: GSH + R-X →GSR + HX. The mammalian soluble GSTs are divided into 4 main classes, alpha (A), mu (M), pi (P), and theta (T). The role of these enzymes in individual susceptibility to chemical exposure and toxicity is difficult to determine because of the large number of isozymes in the body. Second, GST expression varies among tissues. Not all isoforms are found in every tissue or all species. One important example, with respect to methyl bromide, is GSTT which is found in human erythrocytes but not in rodent erythrocytes. Third, GSTs have been found to be polymorphic in the human population. There are individuals who do not have the gene for certain GSTs. It has been determined that 50% of the Caucasian population do not have GSTM1, and 16% do not have GSTM3. GSTT has been found to be

variable among different ethnic groups. The percentages of the population without the GSTT gene ranged from 9.7% (Mexican-Americans) to 64.6% (Chinese-Americans), as cited by Garnier *et al.* (1996). With GSTP, the different variants of the enzyme are due to the transition mutation of a codon (s) such that other amino acids are substituted.

Methyl bromide has been identified as a substrate for GSTT (Eaton and Bammler, 1999). In 1990, Hallier *et al.* (1990) showed that when human erythrocyte cytoplasm was incubated with methyl bromide, there was a loss of methyl bromide in the gas phase with the formation of S-methylglutathione via an enzymatic reaction. Individuals which showed this activity were designated as "conjugators" while those with activity level comparable to boiled erythrocyte cytoplasm were "non-conjugators".

GSH + MeBr → S-methylglutathione + HBr

This interaction of methyl bromide with sulfhydryl groups has been used in the study of methyl bromide workers. Iwasaki *et al.* (1989) and Goergens *et al.* (1994) showed methylcysteine levels in hemoglobin proteins were higher in some methyl bromide workers compared to controls (Details of these studies are in **III.E.4.**). However, a quantitative relationship between adduct level and exposure was not determined.

There is evidence which shows conjugators, individuals with GSTT, may be more protected than non-conjugators from the genotoxicity of methyl bromide. In the study by Hallier *et al.* (1993), methyl bromide was incubated with whole blood from conjugators and non-conjugators. Lymphocytes from conjugators had lower number (range of 6.51 to 7.95) of sister chromatid exchanges per cell than non-conjugators (range of 10.19 to 13.97). The lower level of SCEs in the conjugators, compared to the non-conjugators, was attributed to the reduced amount of methyl bromide available to interact with lymphocyte DNA because of reaction with erythrocyte proteins mediated by GSTT.

On the other hand, there is evidence that shows methyl bromide reaction with GST may be involved in the manifestation of neurotoxicity. In Davenport *et al.* (1992), GST activity was inhibited in the brain of rats exposed to methyl bromide (details in **III.B.1.**). The GST activity was protected when the rats were either pre- or post-treated with an inhibitor of monohalomethane toxicity. In a report of poisoning of two workers, the non-conjugator had fewer neurotoxic effects when compared to the conjugator (Garnier *et al.*, 1996) (details in **III.H.1. Occupational Exposure**). The formation of S-methylglutathione, via conjugation of methyl bromide with GSH, in the brain of the conjugator was hypothesized to be involved in the neurotoxicity. The non-conjugator also had 2-fold higher concentrations of S-methylcysteine adduct in the erythrocytes; but the reaction was considered non-enzymatic. However, in another report of the same study, the worker designated as a conjugator may have been exposed to higher levels of methyl bromide because of an "inefficient" filter mask (Deschamps and Turpin, 1996).

It is unknown how these results on GST polymorphism and genotoxicity may be extrapolated to cancer susceptibility after methyl bromide exposure. First, there is no association between genotoxicity and oncogenicity of methyl bromide in experimental animals. Methyl bromide has been found to be genotoxic in rodents; yet, long-term studies in rodents have not shown methyl bromide to be oncogenic. Second, the relationgship between GST polymorphism on cancer susceptibility remains unclear. While many studies showed a role for

GST enzymes in the detoxification of chemicals, there are few studies on the relationship between GST and cancers (d'Errico *et al.*, 1999); however, most of these studies have limited number of subjects. In the epidemiological studies reviewed, there was no association between GSTT1 polymorphism and the risk of bladder cancer, lung cancer and gastric cancer (d'Errico *et al.*, 1999). When GST polymorphism was combined with smoking as a factor, some reported association with between GSTM1 and GSTT1 null genotypes with the risks of lung, bladder and colon cancers (Strange and Fryer, 1999). However, other studies showed contrary results (Strange and Fryer, 1999). The potential influence of GSTT activity on cancer susceptibility is further complicated by the role of other isozymes of GST and other enzymes in the activation and/or detoxification of the substrate. The combination of GSTM1 null and CYP1A1 rare alleles have been associated with increased cancer risk due to smoking (Fryer and Jones, 1999).

In conclusion, the data show that the interaction of methyl bromide and GST is complex. While the polymorphism of GSTT in the human population is important to consider, it is not possible to conclude that GSTT polymorphism leads to increased susceptibility to methyl bromide toxicity and to determine whether or not the variation is sufficiently addressed by the 10-fold default intra-individual uncertainty factor.

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (U.S. EPA, 1997b and c). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NRC, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

In recent documents, U.S. EPA used 3 criteria for the determination of the factor: (1) completeness and reliability of the toxicology database, (2) completeness and reliability of the exposure database, and (3) potential pre- and post-natal toxicity (U.S. EPA, 1999 a, b, and c). The latter criterion requires the consideration of evidence for developmental and reproductive toxicity, and developmental neurotoxicity.

V.E.1. Pre- and Post-natal Sensitivity

In recent years, issues have been raised on the adequacy of the risk assessment process to address the potential increased sensitivity of infants and children to pesticides. The basis of this concern was discussed in detail in the 1993 National Research Council report: *Pesticides in the Diets of Infants and Children* (NRC, 1993). In the 1994 DPR report: *A Joint Review of Existing Federal and State Pesticide Registration and Food Safety Programs* (also known as the PECC report), the PECC recommendation was to address the susceptibility issue on a case-by-case basis when specific data become available (DPR, 1994). A review of recent time-limited tolerances for pesticides showed that U.S. EPA generally applied an additional

uncertainty factor of 10 for an incomplete database where one or more FIFRA required reproductive or developmental toxicity studies were not available. An additional uncertainty factor of 3 (MOE of 300) was used when the NOEL for developmental or reproductive effects was lower than that for maternal toxicity, or when there was no developmental neurotoxicity study. The criteria for the developmental toxicity testing included findings of teratogenicity to the central nervous system, neuropathology and neurotoxicity, hormone-like activity, and developmental toxicity (for effects other than structural abnormalities of the CNS) (Levine and Butcher, 1990). USEPA recently proposed that a development neurotoxicity study be included in the core toxicology data set (U.S. EPA, 1998c).

There was some evidence for increased sensitivity to the prenatal and post-natal toxicity of methyl bromide when NOELs for developmental or reproductive toxicity were compared with those for maternal toxicity. In the rabbit developmental toxicity study, the NOEL was 20 ppm for both effects in the fetus and neurotoxicity in the dam (Breslin *et al.*, 1990b). However, it should be noted that the neurotoxicity was observed toward the end of the experiment while effects on the fetus were likely to have occurred earlier during organogenesis. In the developmental study conducted with rats, increased incidence of delayed skull ossification was reported in rat fetuses with a NOEL of 20 ppm compared to a NOEL of >70 ppm for maternal toxicity (Sikov *et al.*, 1981). In the rat reproductive toxicity study, the NOEL was 3 ppm for reduced fertility in the F2b mated rats and for effects in the pups (decreased pup body weights and organs weights) (American Biogenics Corp., 1986). It is not known whether the reduced fertility in these F2b rats was due to exposure as adults or a manifestation of effects from previous *in utero* exposure (as fetuses from the F1 mating).

There may be a potential for increased sensitivity of infants and children to the neurotoxicity of methyl bromide based on consideration of the maturity of the central nervous system. In the young, the central nervous system is not fully developed at birth. Neuron proliferation and migration, blood-brain barrier, synaptic connections, as well as receptor and transmitter systems development continue after birth and into childhood (Rodier, 1995). Furthermore, there is a difference in the maturity of the brain development between laboratory animals and humans (Hoar and Monie, 1981; Dobbing and Sands, 1973). At birth, the rat brain is considered to be more developed than the human brain.

The potential impact of methyl bromide on the developing nervous system has not been evaluated. The toxicity studies for methyl bromide have only been conducted with adult animals and a developmental neurotoxicity study is not available. There is one case report in humans which showed that methyl bromide is more toxic to the young. In an acute exposure to methyl bromide in a home, an infant died while the parents recovered without apparent neurological deficits (Langard *et al.*, 1996). It is not known whether the severity of the effects on the infant was from increased exposure due to physiological differences (*i.e.* increased respiration rates) or increased sensitivity. Another concern is the potential cumulative toxicity from low level exposure to methyl bromide. As discussed in **IV.A.1.b. Neurotoxicity**, the dogs with prior exposure to relatively nontoxic level of methyl bromide (11 ppm) showed decreased activity earlier than those with no previous exposure when both groups were exposed to similar methyl bromide levels (156-158 ppm).

In this risk assessment for methyl bromide, inter-individual differences were accounted for by an uncertainty factor of 10. Given that methyl bromide is a potent neurotoxicant and there

are inadequate toxicity information for infants and children, it may be prudent to consider an additional uncertainty factor to address the potential increased sensitivity for these population subgroups. However, the NRC in the review of the draft RCD/1999 concluded that the available database was sufficient to identify appropriate NOELs for risk characterization (NRC, 2000). Furthermore, the NRC indicated that this additional uncertainty factor was not necessary since the DPR selected NOELs for risk characterization were adequately conservative.

V.E.2. Aggregate Exposure

There could be a potential for aggregate exposure from occupation or residential exposures and dietary exposures. The risk characterization for aggregate exposure is in Volume III.

V.E.3. Cumulative Toxicity

Since the mechanism of methyl bromide toxicity is possibly due to alkylation of reactive groups, there is potential cumulative toxicity between methyl bromide and other chemicals with such a general mechanism of toxicity. The approach to address the cumulative risk of chemicals is being discussed by the U.S. EPA Scientific Advisory Panel. The main focus of the discussion at this time is the toxicity of organophosphate pesticides.

V.E.4. Endocrine Effects

Based on the studies reviewed, methyl bromide has not been shown to cause endocrine disruption effects.

VI. CONCLUSIONS FOR INHALATION EXPOSURE

The human health risk from potential inhalation exposure to methyl bromide was evaluated in this Volume I of Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: developmental toxicity for acute exposure, neurotoxicity for short-term and subchronic exposures, and tissue damage to the nasal cavity for chronic exposures. For acute and chronic exposure endpoints, neurotoxicity was also considered in the determination of the critical NOELs. The risks, expressed as the margins of exposure, were calculated for workers and residents involved or living in the vicinity of structural, field and commodity fumigations. Generally, a MOE of at least 100, which takes into account the possibility of 10-fold variations in susceptibility within the human population as well as between laboratory animals and humans, is considered adequate to protect humans from the effects of concern. Exposure scenarios with MOEs of less than 100 should be considered in the risk management process.

With structural fumigation, the acute MOEs for workers and residents were assumed to be at least 100 based on restrictions in the DPR regulations. However, data are needed to estimate actual exposures for acute and short-term exposures for workers and residents.

For field fumigation, the acute MOEs for workers were at or greater than 100 because of the most effective equipment modifications and work hour restrictions were placed in DPR regulations. However, there were work tasks with acute and short-term MOEs of less than 100 which are not specifically excluded in the regulations. They were: disc driver (acute MOE of 22, deep shank injection), and tractor drivers and basket-men in tarp removal (acute MOE of 20-21, tarp shallow with Noble plow shanks). For subchronic exposure, most of the worker tasks had MOEs of less than 100; many were less than 10 and included applicators, copilots, disc drivers, and tarp removers. The MOE for workers at adjacent fields was assumed to be 100 since they work outside of the buffer zone. Actual data are needed to verify this assumption as analyses for the effectiveness of buffer zones showed MOEs of less than 100 for some applications (in particular large fields and certain emission rates). For residents living at the buffer zone perimeter of fumigated fields, the acute MOEs were generally around 100 for the 95th percentile exposure except for a MOE of 91 for 30 acres and 80 lbs emission rate, and MOEs of 89-95 for 40 acres and all emission rates. The acute MOEs were generally greater than 100 at the 90% percentile exposure. No assessment was conducted for repeated exposures.

For commodity fumigation, the acute MOEs for workers involved in fumigation were at 100 because DPR regulation set work hour restrictions to limit the maximum exposure at 210 ppb. The actual MOEs were likely higher as the upper limit may not be reached in some scenarios. The short-term MOEs were greater than 100 for all work tasks based on actual measurements; the only exception was a MOE of 67 for the task of cleaning plant. The MOE was also 67 when the daily exposure was set at 210 ppb for raisin (clear chamber) and walnut (vacuum chamber) workers. The subchronic and chronic MOEs were generally less than 100 based on measured values and exposures amortized from 210 ppb.

For workers doing other tasks in commodity fumigation facilities, the acute MOEs and many of the short-term MOEs were at or greater than 100. The only exception was the short-term MOE of 67 for workers at the sorting or packaging areas and their exposures were based on 210 ppb as daily exposure. The subchronic and chronic MOEs for all workers were at or less

than 67. Additional data are needed to characterize the exposures of these workers at the facilities. For residents living near fumigation facilities, the MOEs for all durations were based on 210 ppb used for acute exposure, and not actual measurements. The MOEs were between 1 and 78 for short-term, subchronic and chronic exposures.

The ambient air monitoring of three counties in California showed acute and short-term MOEs greater than 400. However, the 7-8 week MOEs were less than 100 (MOEs of 13 to 78) in some locations. Additional monitoring are being conducted to better characterize these exposures.

This risk assessment concluded that human inhalation exposure to methyl bromide resulted in margins of exposure of greater than 100 in some scenarios but less than 100 in other scenarios. The significance of these MOEs need to be viewed in the context of the limitations and uncertainties discussed. Many scenarios were based on exposure data with few samples or assumed exposure levels (i.e. 210 ppb for acute exposure). There were also scenarios which were not addressed in this document. Additional exposure data are needed to better characterize the exposure. In addition, the overall risk from methyl bromide exposure should consider the risks from other exposure routes. The risk characterization of dietary exposure and aggregate exposure is in Volumes II and III, respectively.

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VIII. ATTACHMENTS